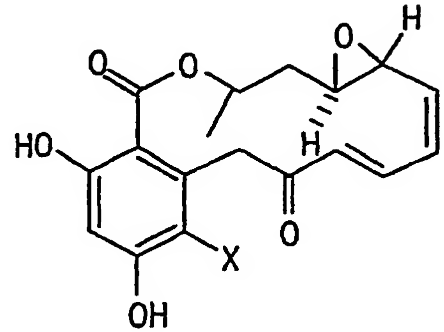
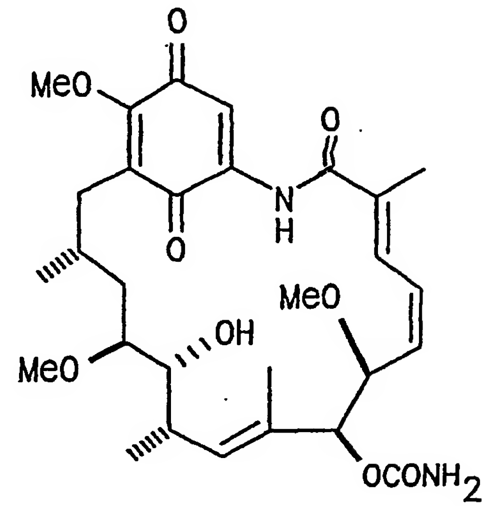
FIG. 1



X=Cl Radicicol (1)
X=H Monocillin I (2)



Geldanamycin (3)

FIG.2

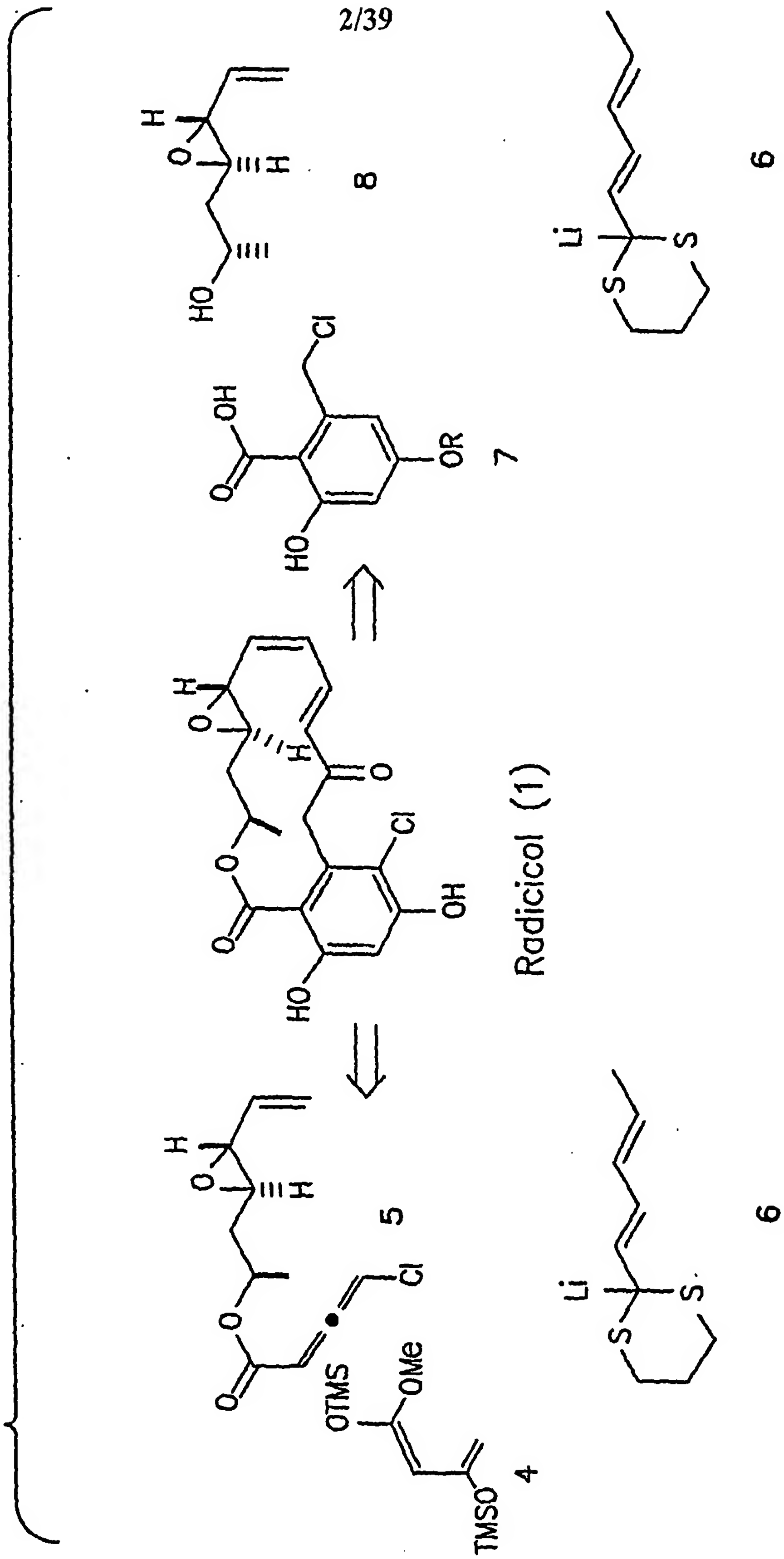
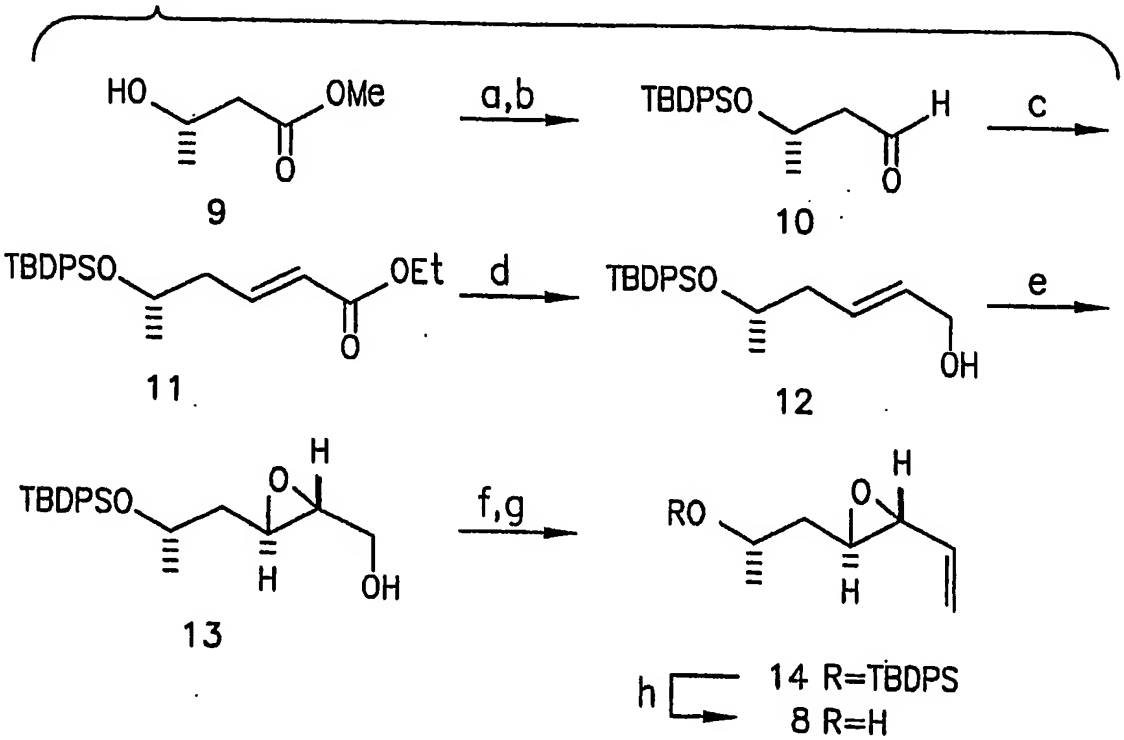


FIG.3



(a) TBDPSCl, imid.,>95%; (b) DIBAL−H,−78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL−H, −20 °C, 96%; (e) (+)−DET, Ti(O*i*Pr$_4$), TBHP,90%,>95%ee; (f) SO_3*pyridine, Et_3N, DMSO, 90%; (g) PH_3PCH_3Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

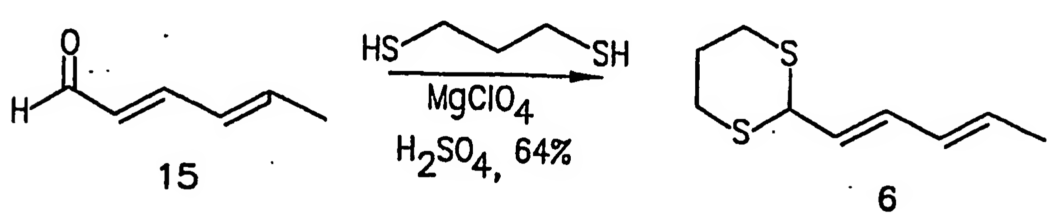
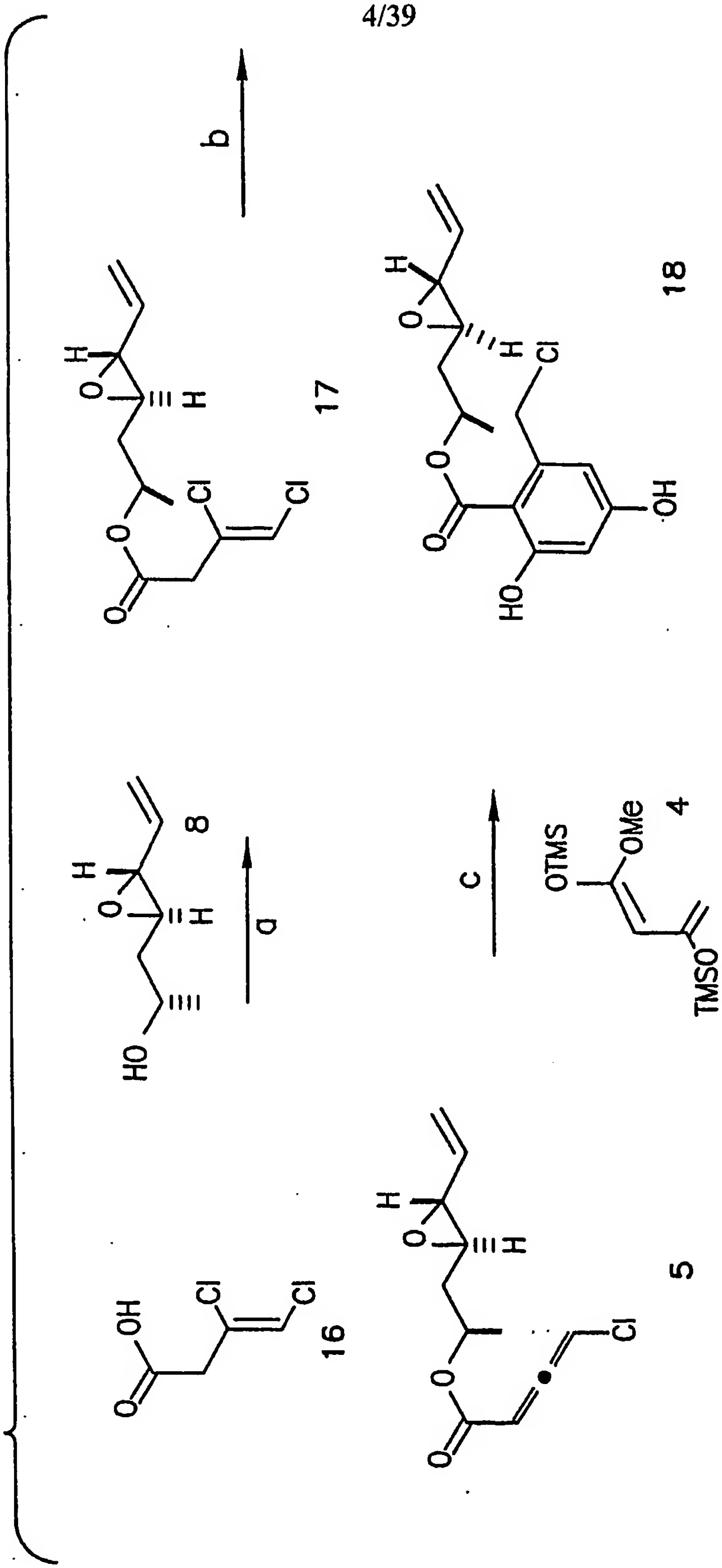


FIG. 4



(a) DEAD, PPh_3, 70%; (b.) iPr_2NEt, 70%; (c.) 50% (4:1)

FIG.5

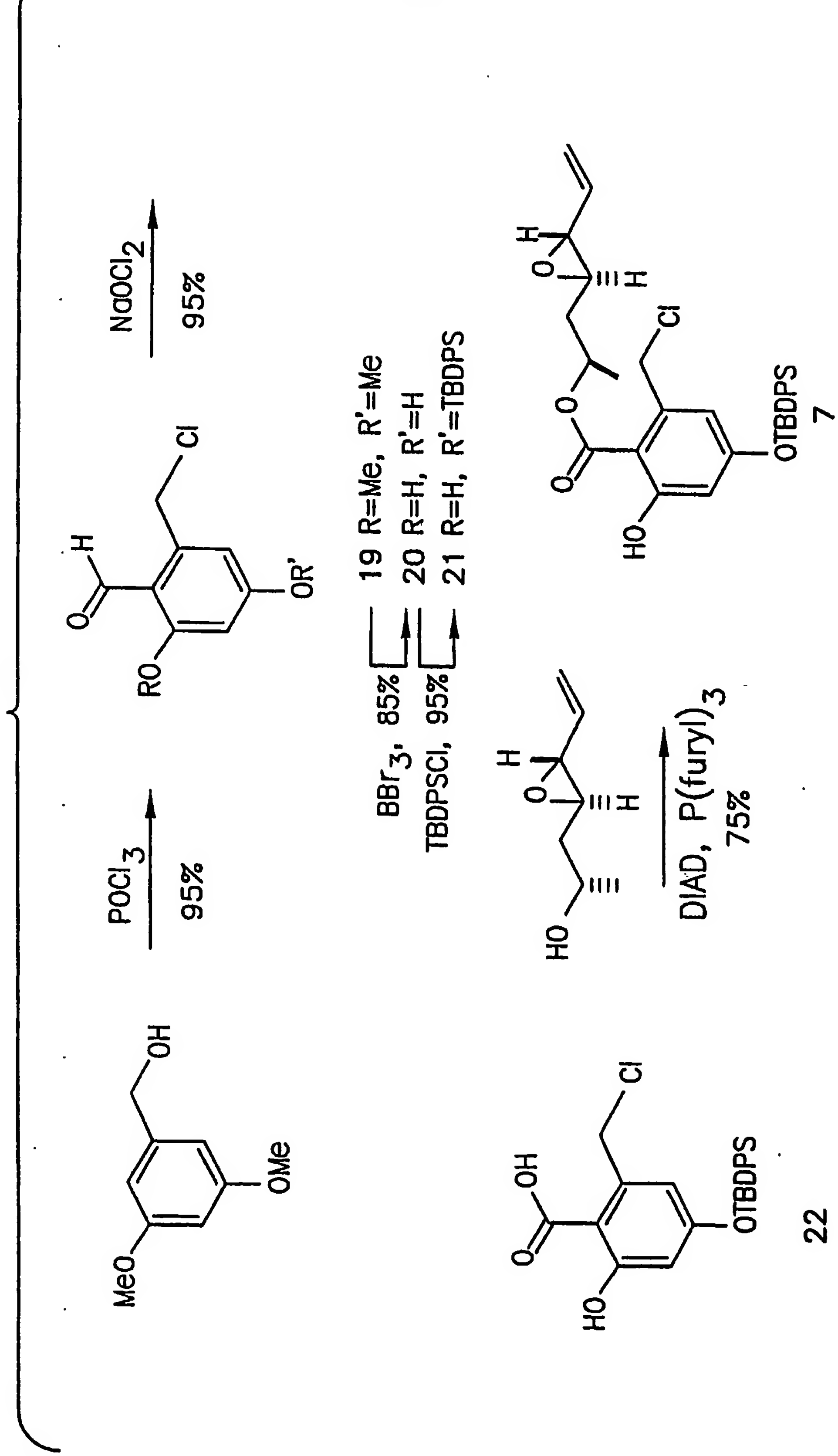
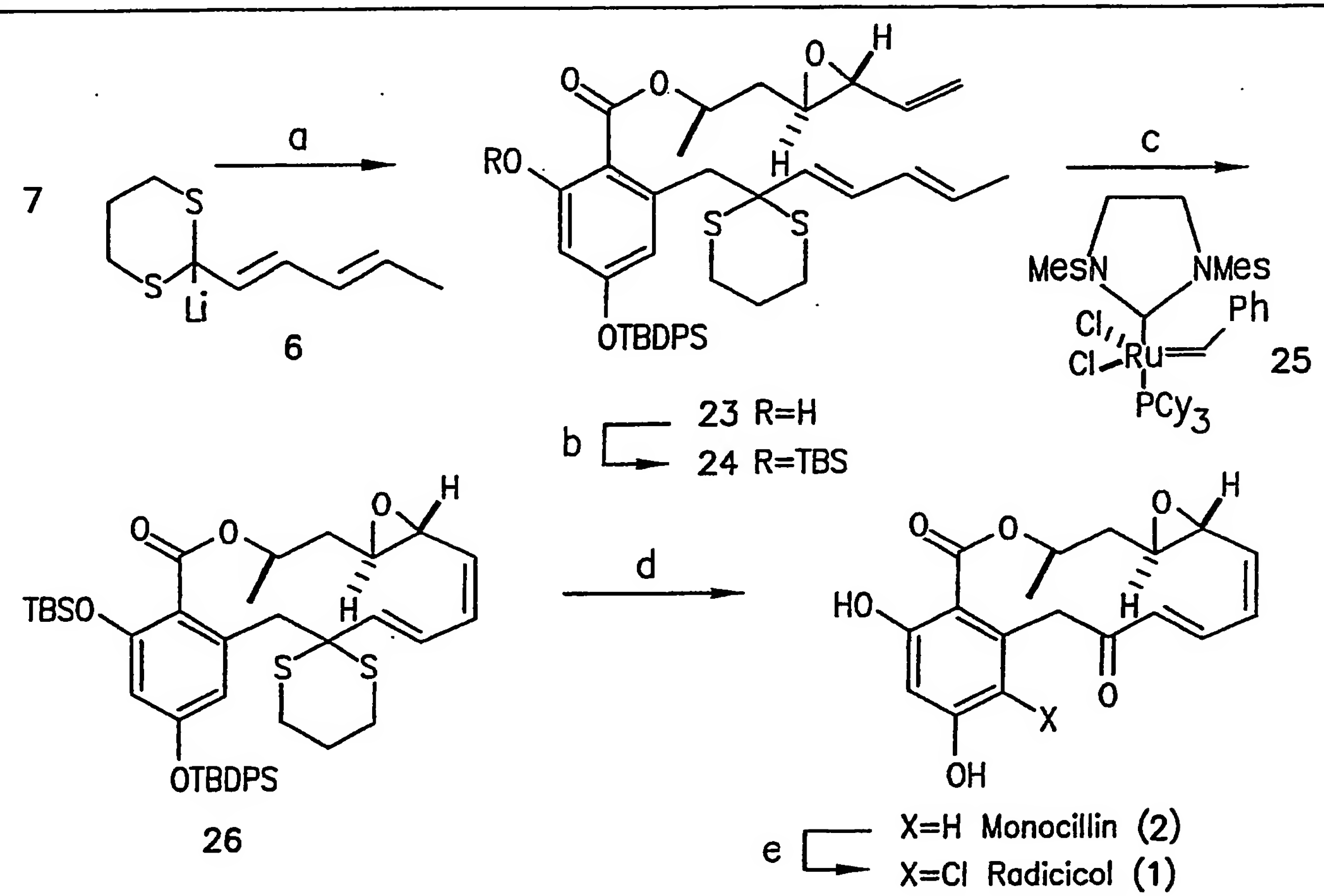

MeO
OMe
OH
POCl3
95%
RO
OR'
H
O
Cl
NaOCl2
95%
BBr3, 85%
TBDPSCl, 95%
19 R=Me, R'=Me
20 R=H, R'=H
21 R=H, R'=TBDPS
HO
O
OH
OTBDPS
22
DIAD, P(furyl)3
75%
OTBDPS
7

FIG.6



a. n−BuLi, −78 °C, 50% (6:1); b. TBSCl, 83%; c. 42 C, 70%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 °C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 50%

FIG. 7

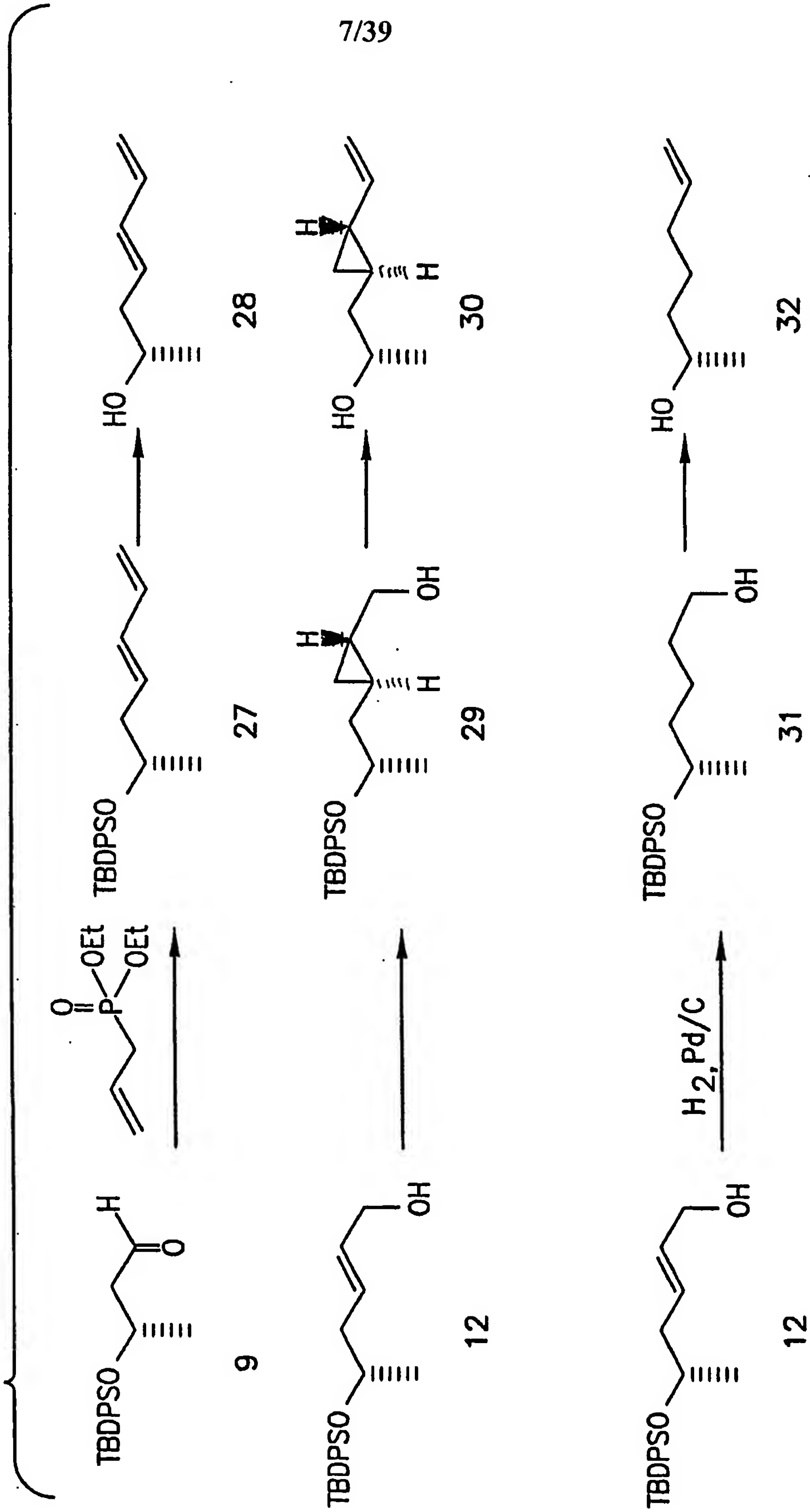
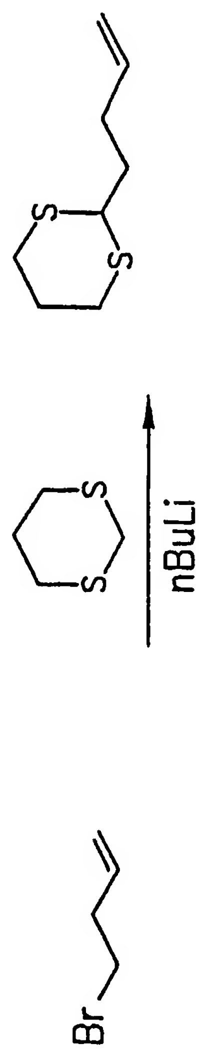


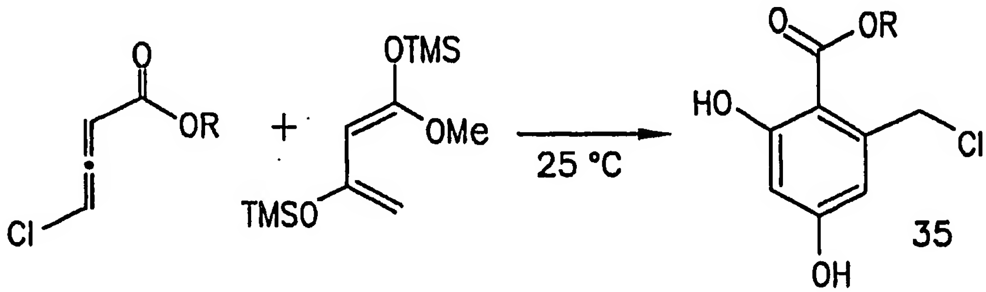
FIG.8



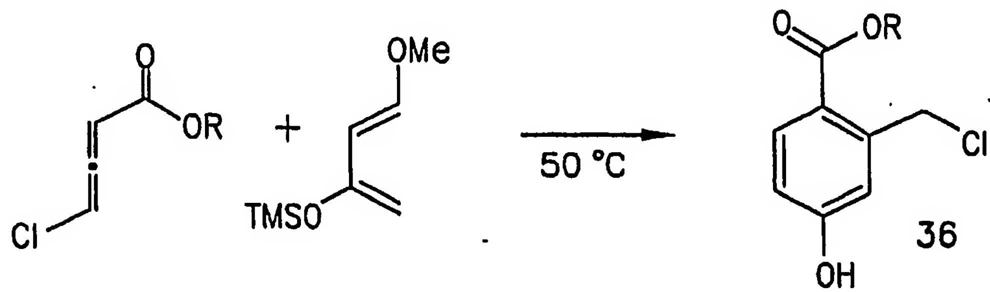
33

34

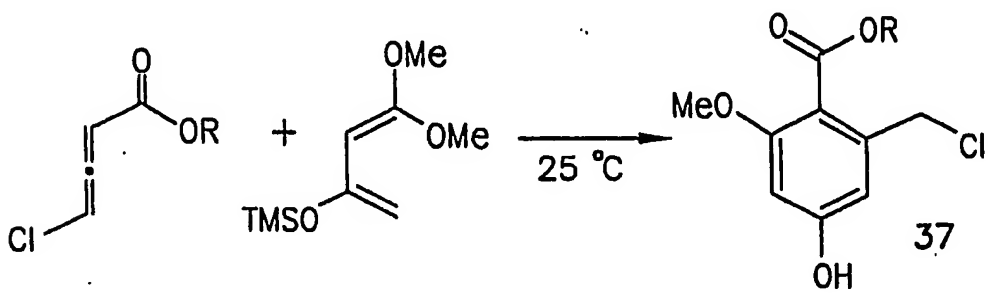
FIG. 9



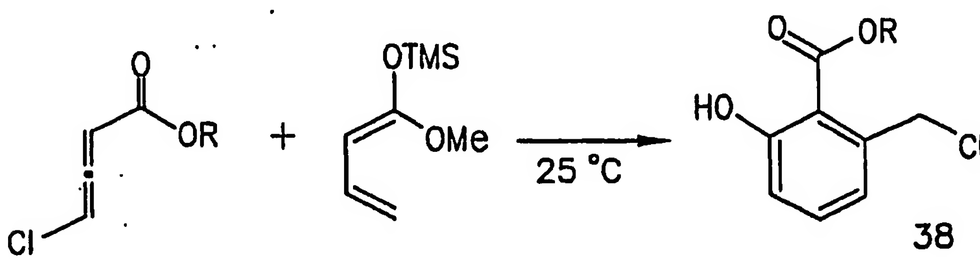
35



36

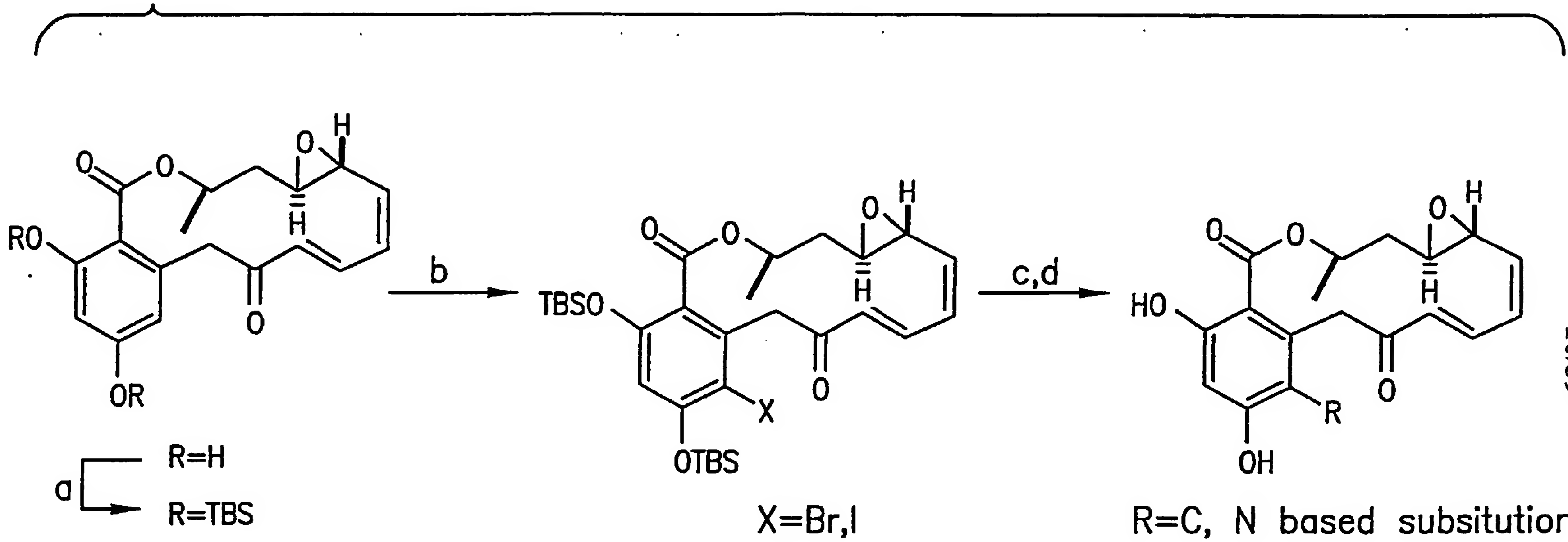


37



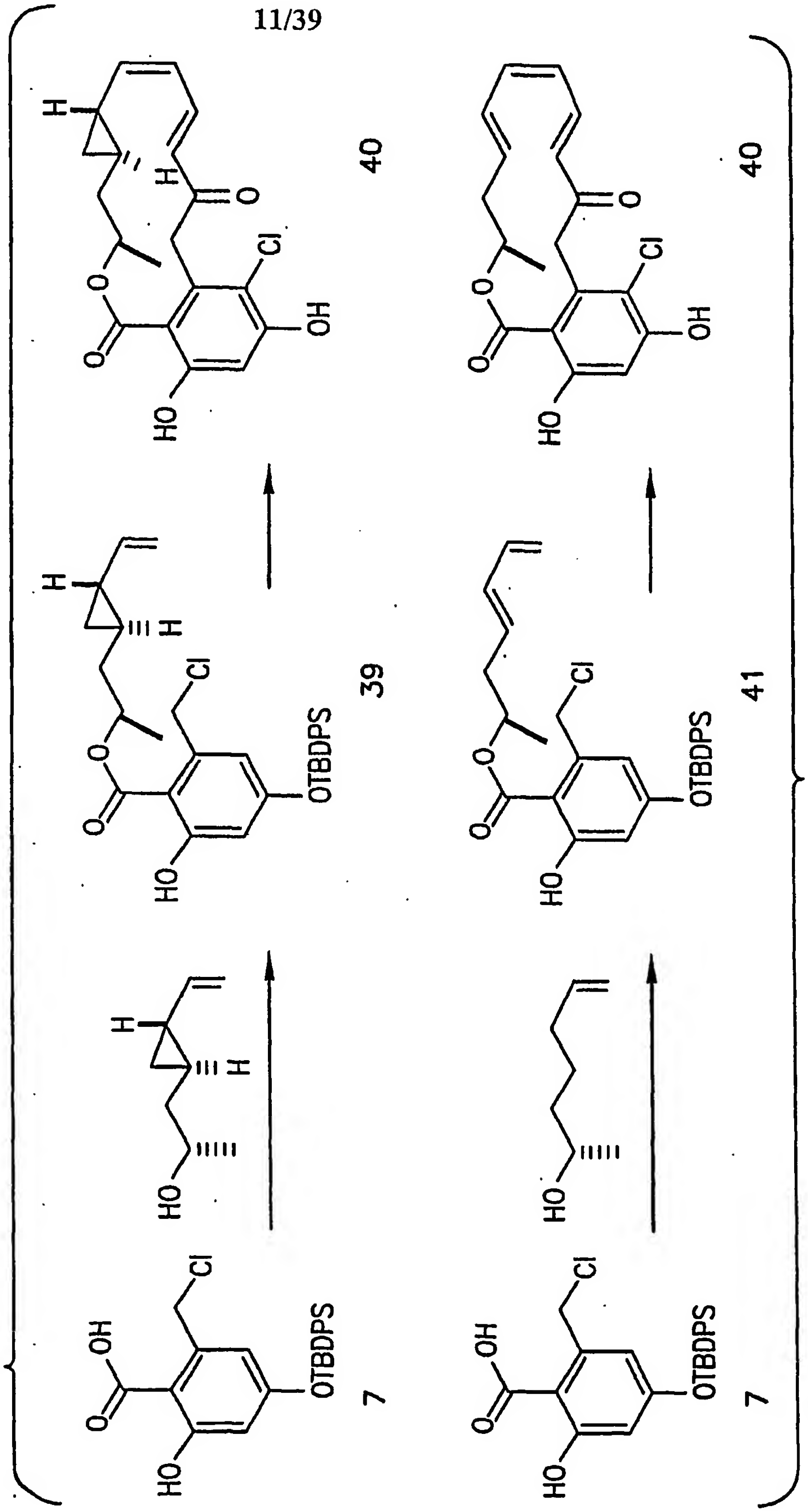
38

FIG. 10



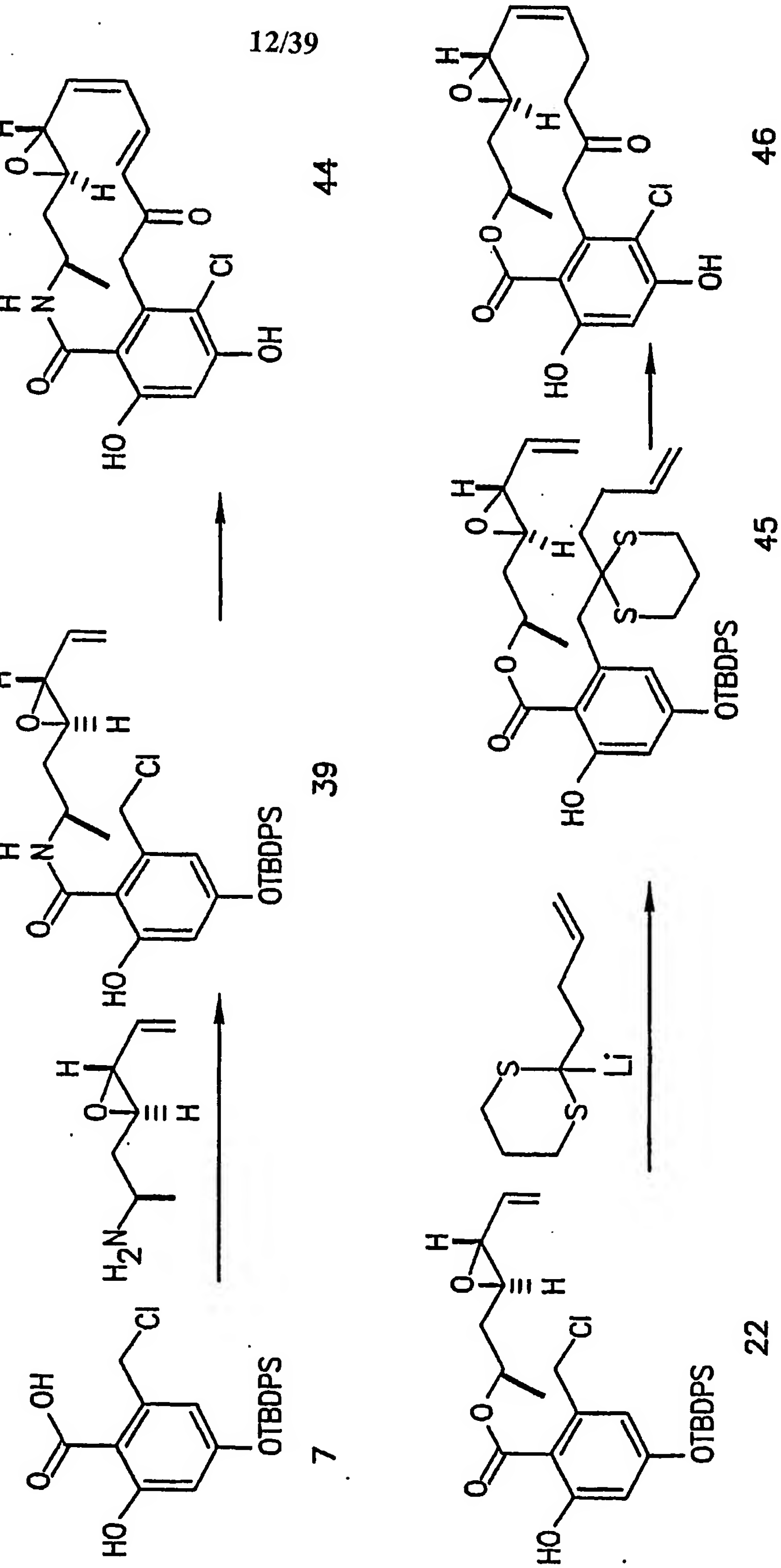
a. TBSCl, pyridine; b. NIS or NBS, TsOH; c. $Pd(PPh)_3$, $RSnBu_3$, d. nBu_4NF

FIG. 11-1



TO FIG. 11-2

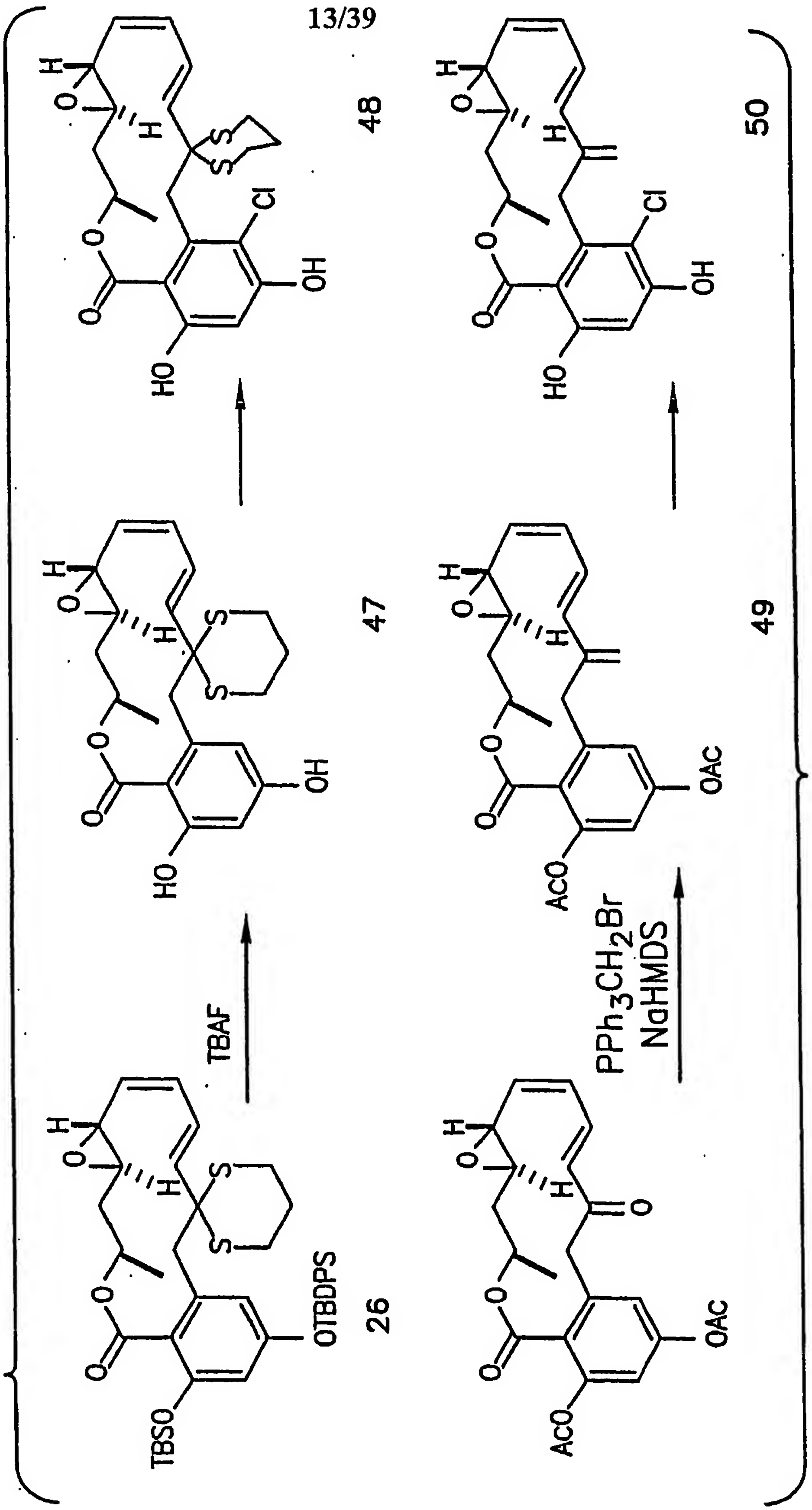
FROM FIG. 11-1



7 39 44 22 45 46

FIG.11-2

FIG. 12-1



26 47 48

49 50

TO FIG. 12-2

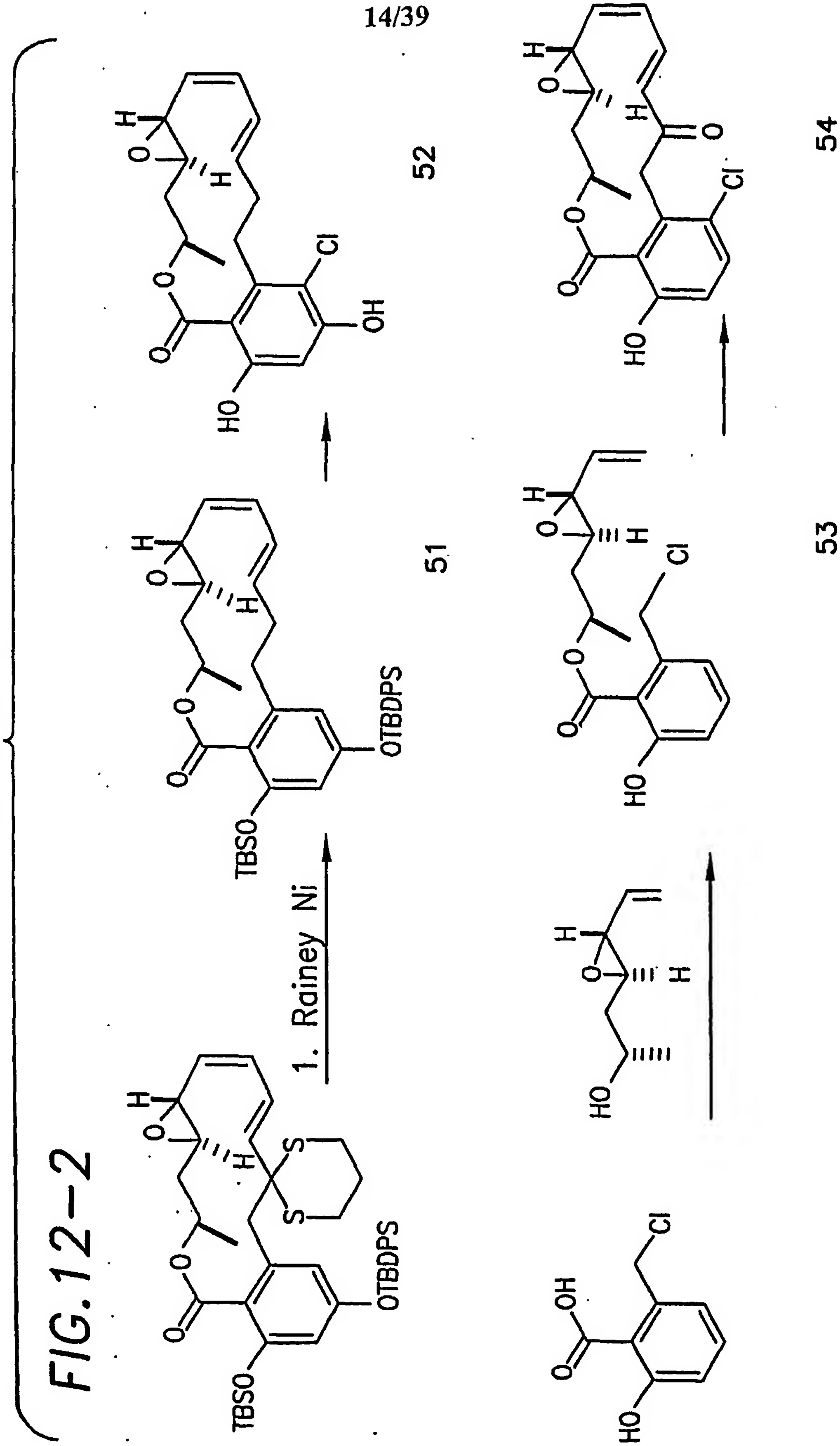
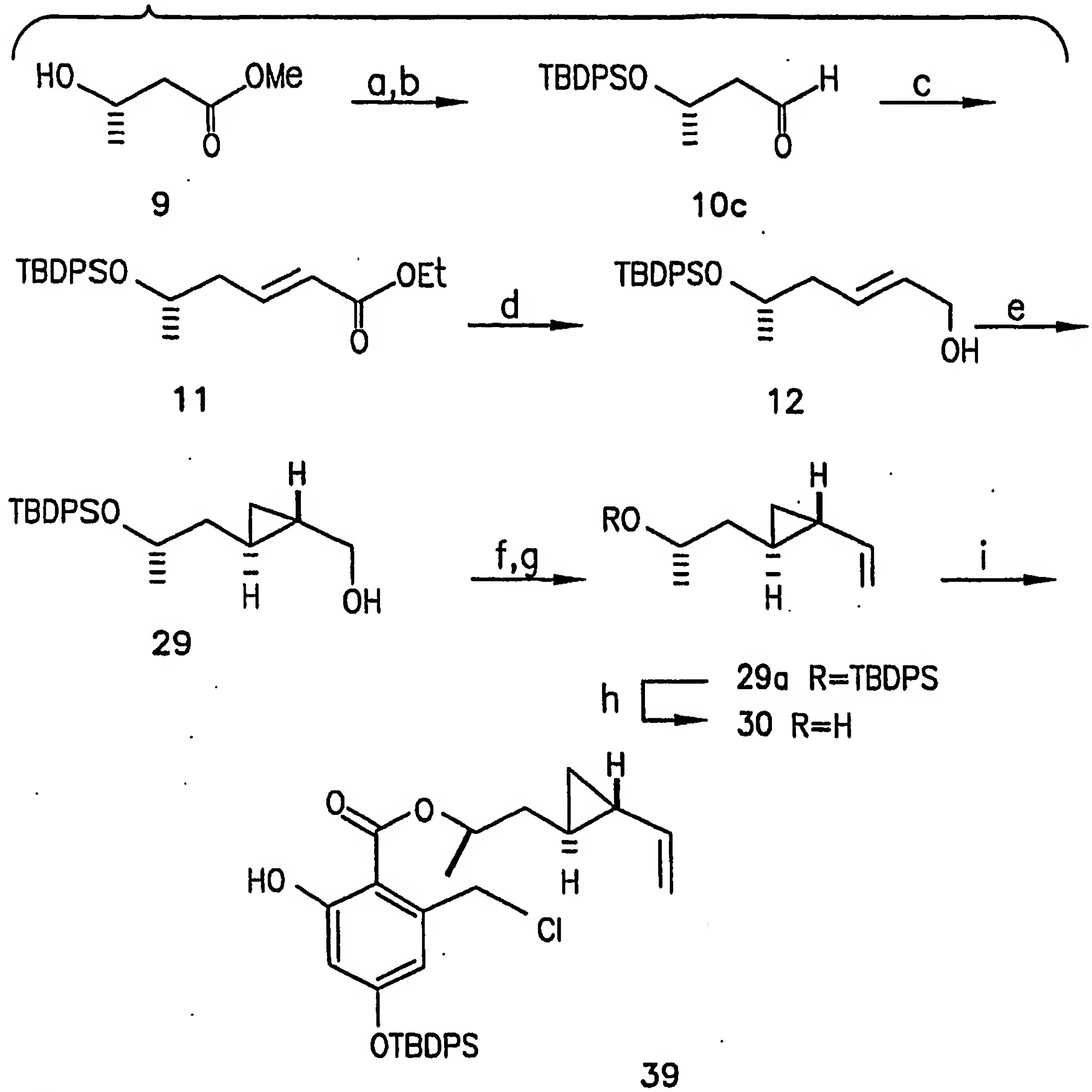


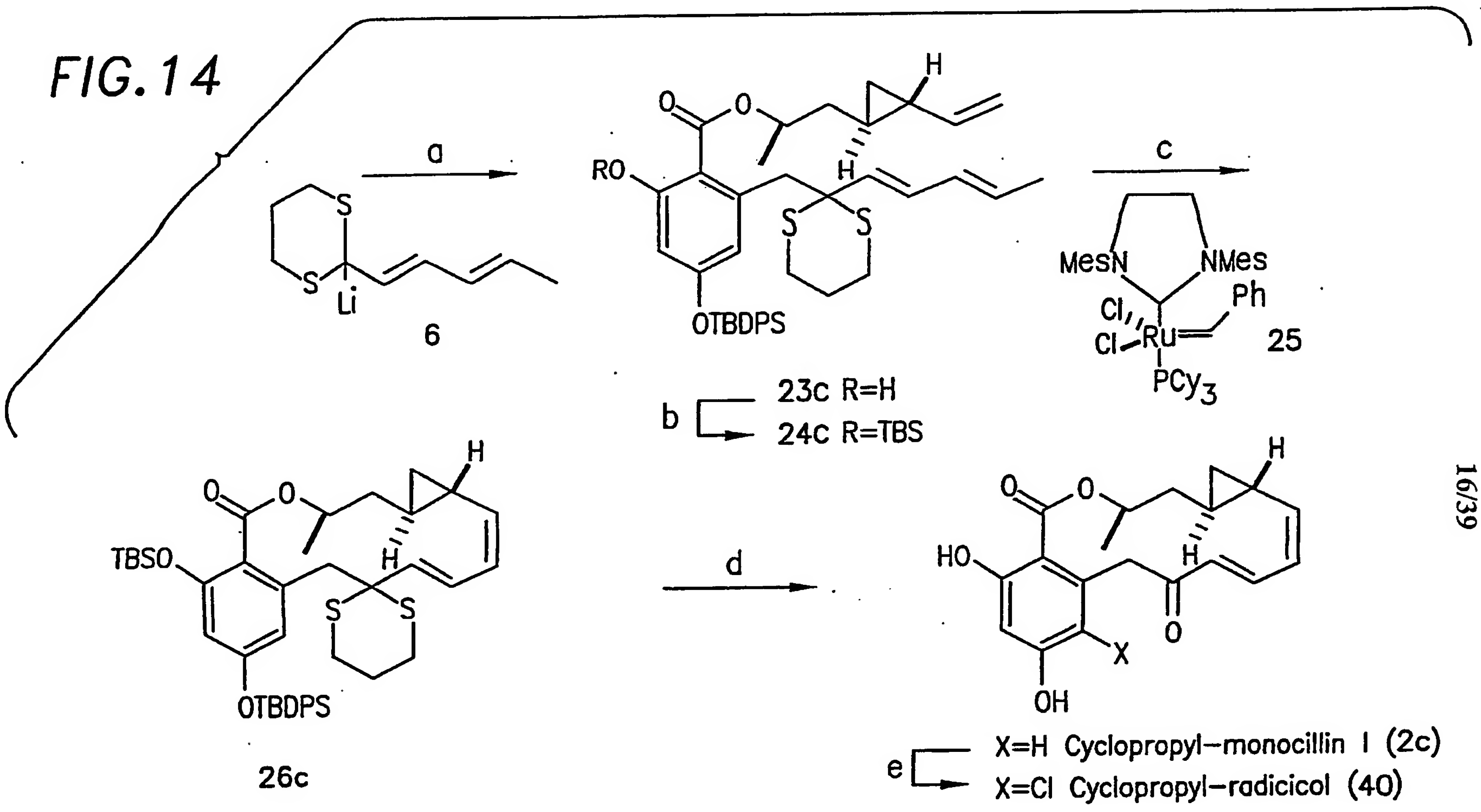
FIG. 12-2

FIG. 13



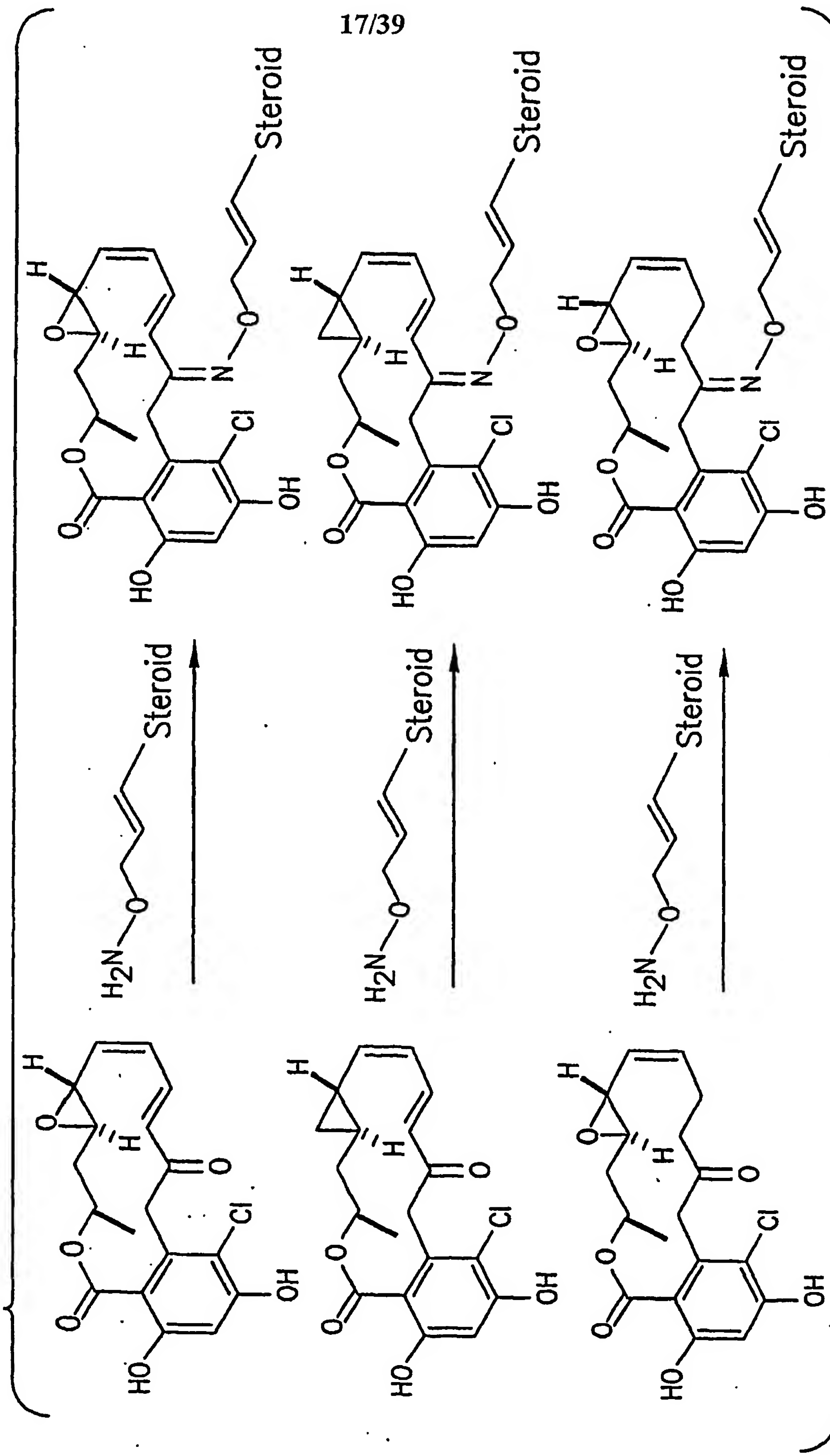
[a] (a) TBDPSCl, imid.,>95%; (b) DIBAL–H,–78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL–H –20 °C, 96%; (e) (+)–tetramethyltartaricacid diamide–BBu, Et_2Zn, CH_2I_2, 9 >95% ee; (f) SO_3*pyridine, Et_3 N, DMSO, 90%; (g) Ph_3 PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7, $P(furyl)_3$, DIA benzene, 60%

FIG. 14



a. n-BuLi, −78 °C, 75% (3:1); b. TBSCl, 83%; c. 42 °C, 20%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 °C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 80%

FIG. 15-1



TO FIG. 15-2

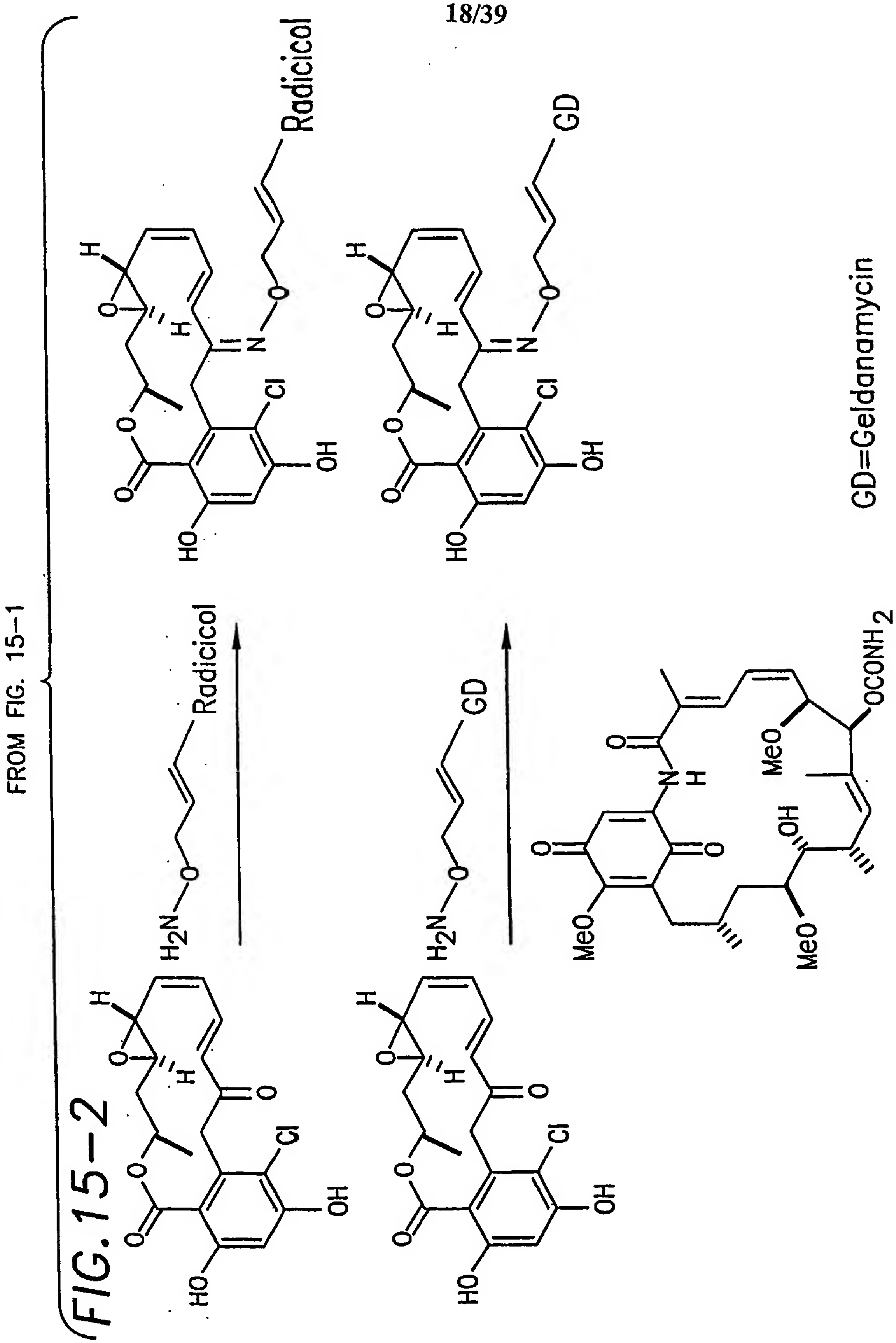
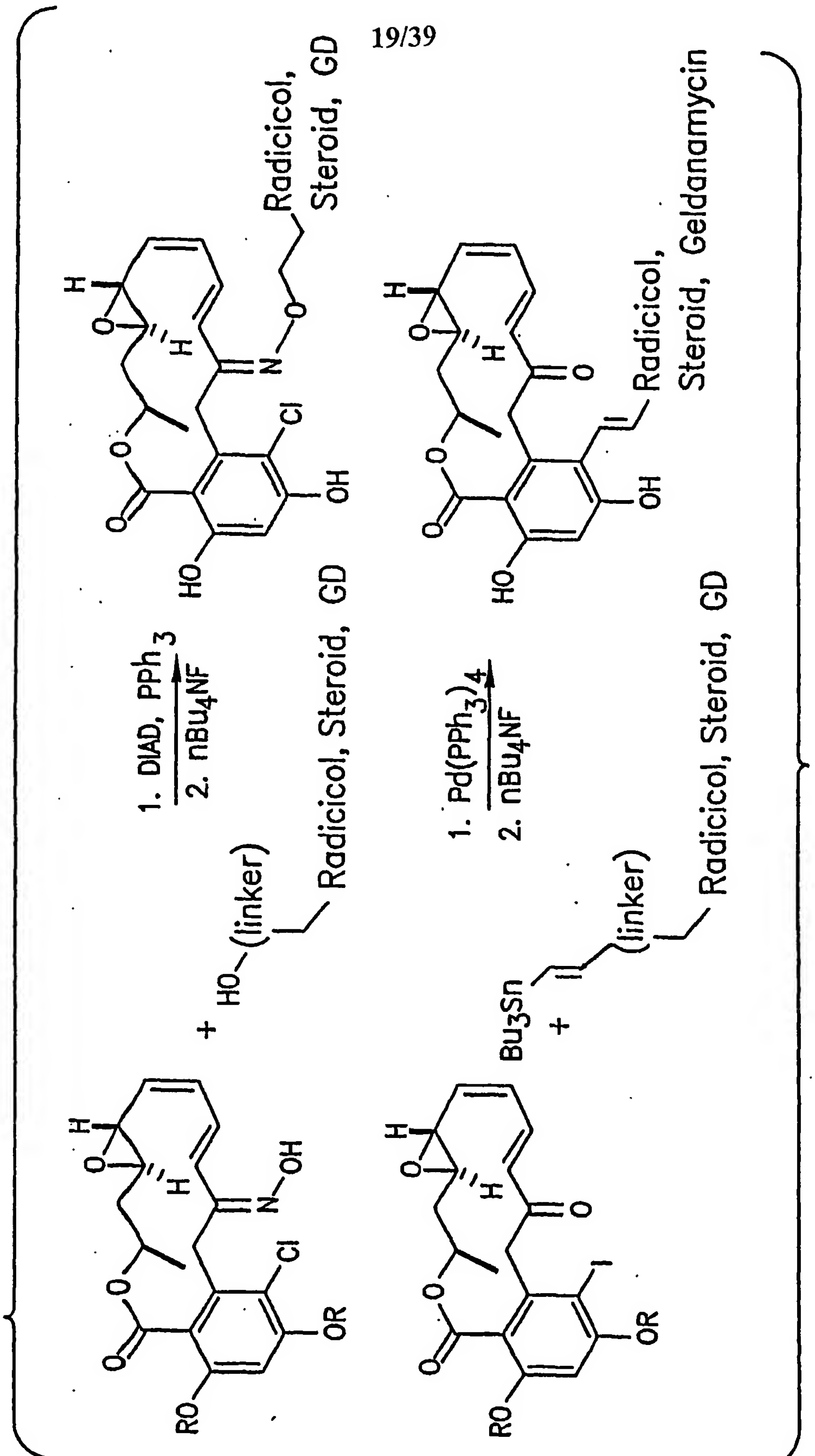


FIG. 15-2

FIG. 16-1



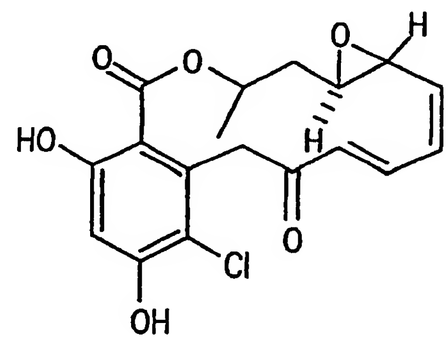
TO FIG. 16-2

FROM FIG. 16-1

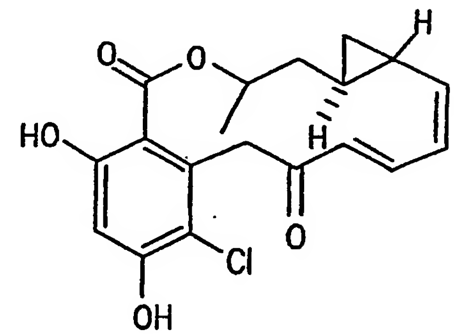
FIG.16-2

FIG. 17-1

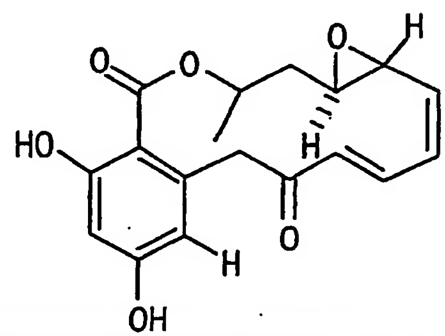
I. Radicicol



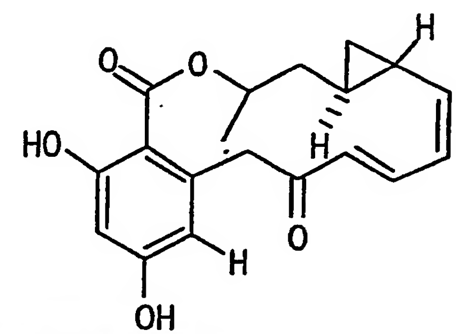
III. Cyclopropyl radicicol



II. Monocillin I



IV. Cyclopropyl monocillin

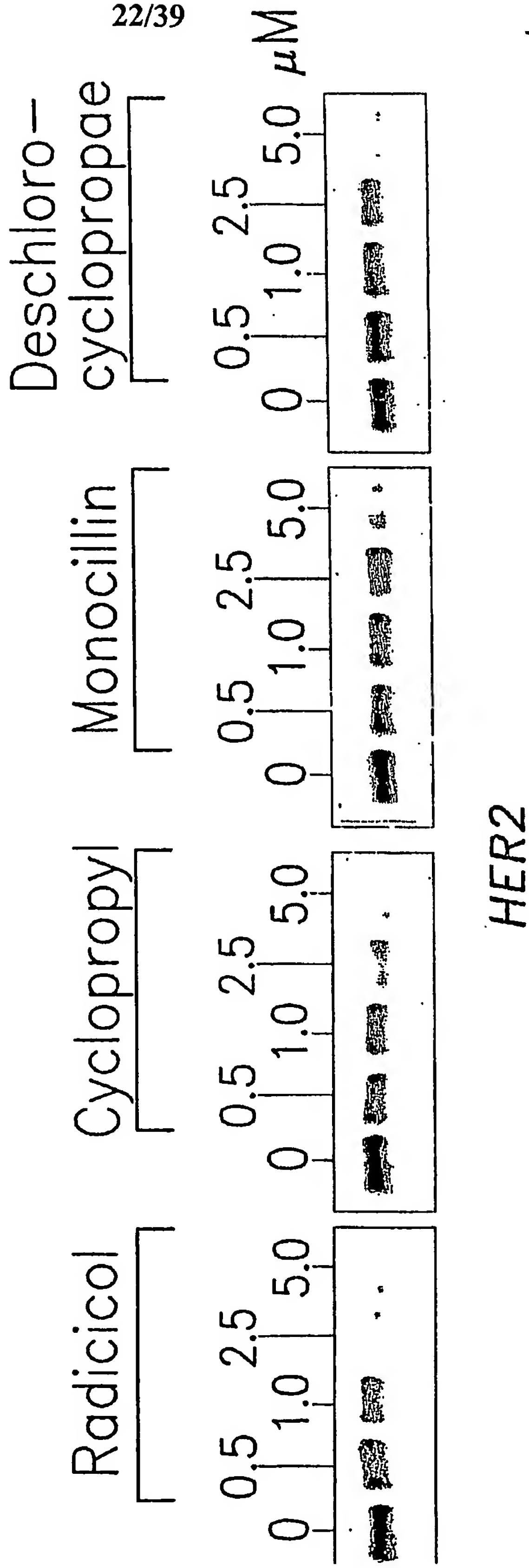


TO FIG. 17-2

FROM FIG. 17–1

FIG.17–2

MCF7 Cells Treated with Radicicol and Analogues

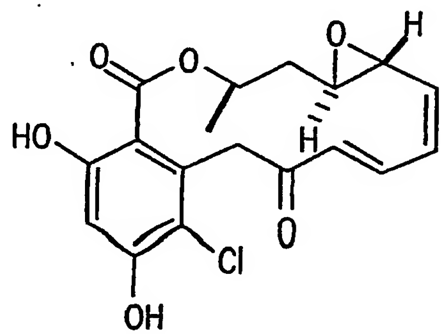


TO FIG. 17–3

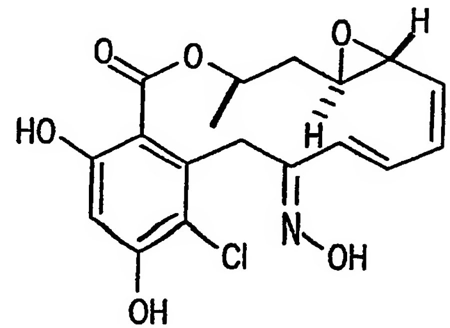
FROM FIG. 17-2

FIG. 17-3

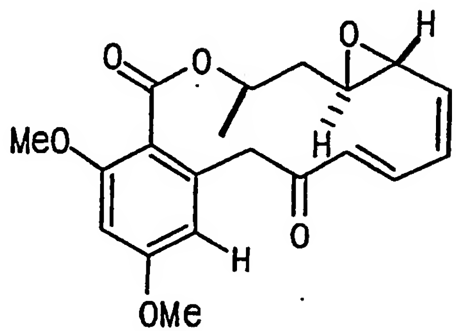
I. Radicicol



VII. Radicicol Oxime



V. Dimethyl Monocillin I



VI. Dimethyl Radicicol

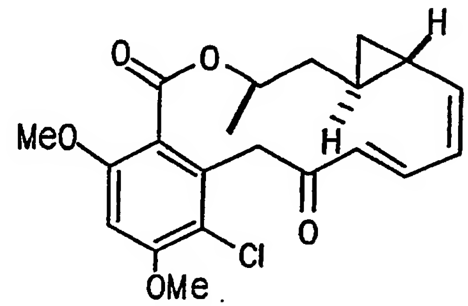
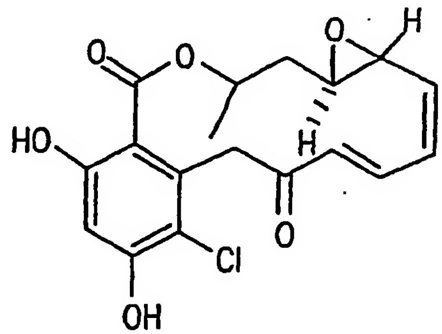
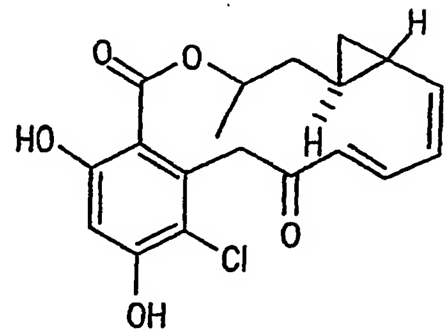


FIG. 18-1

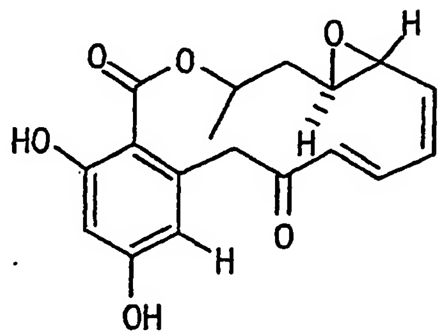
I. Radicicol



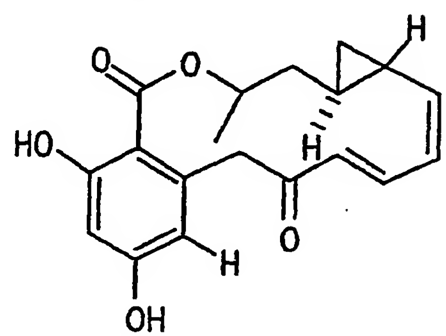
III. Cyclopropyl radicicol



II. Monocillin I



IV. Cyclopropyl monocillin

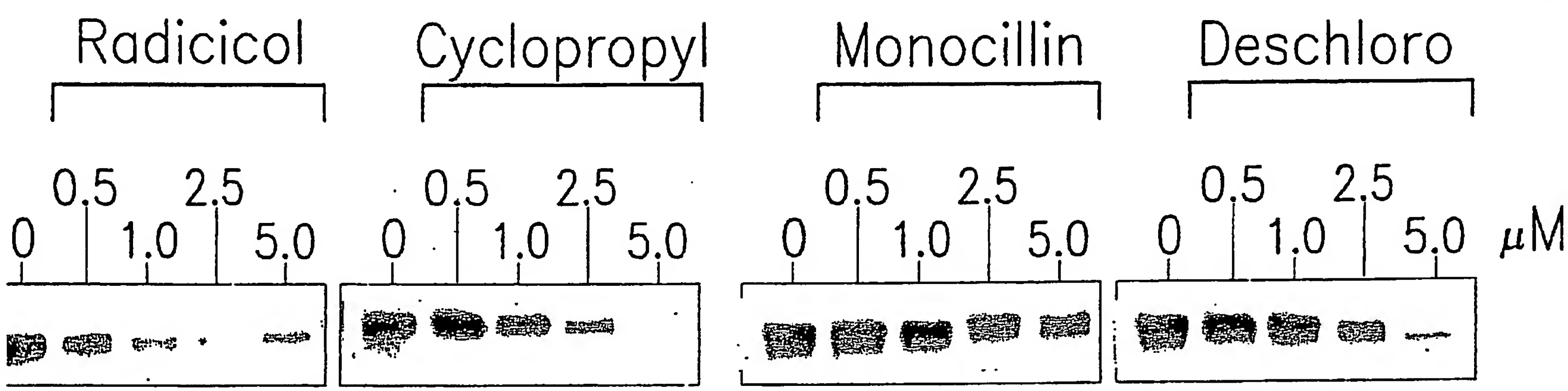


TO FIG. 18-2

FROM FIG. 18-1

FIG. 18-2

BT474 Cells Treated with Novel Radicicols (24hrs.)



HER2

FIG.19

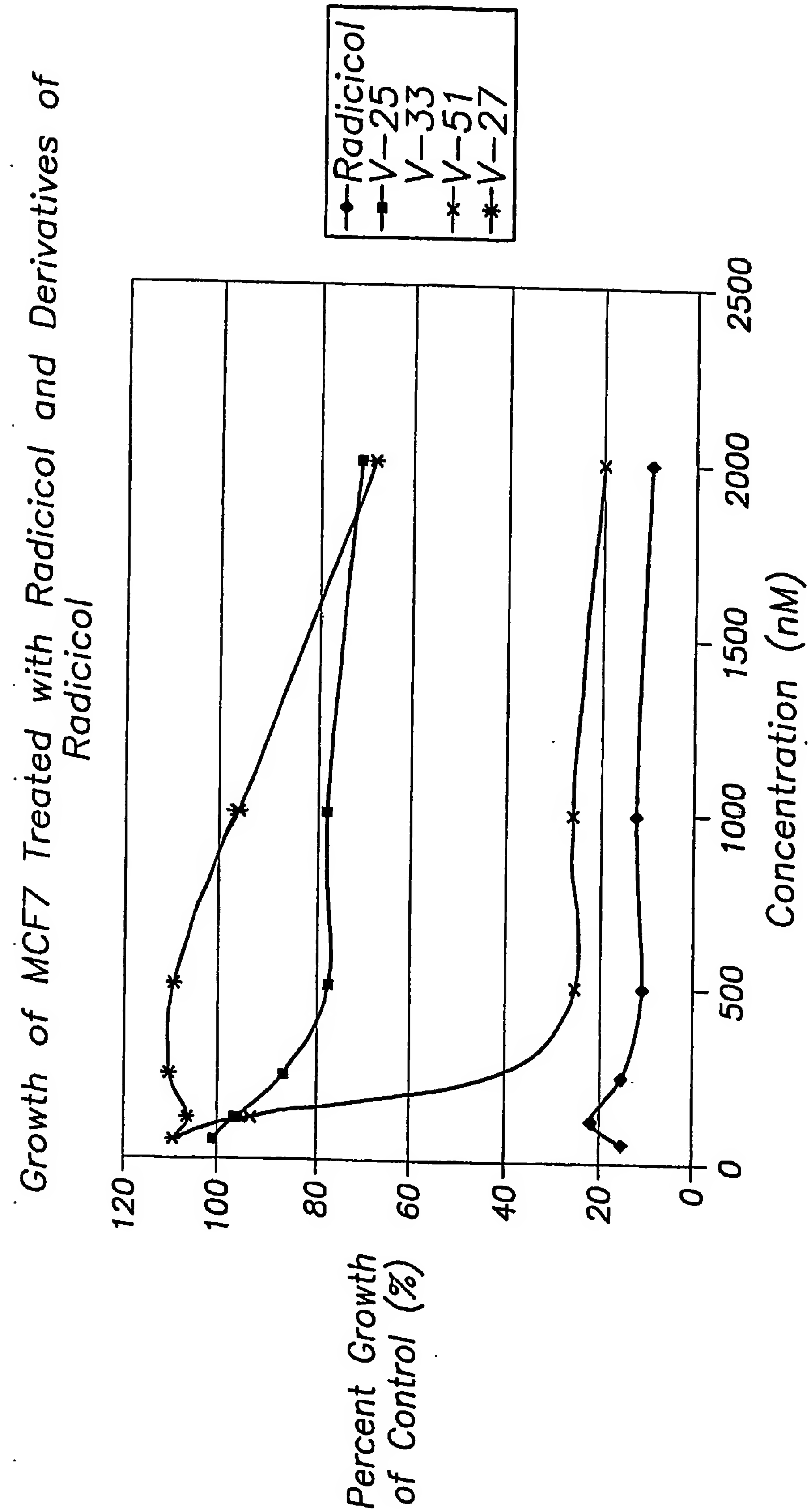

Growth of MCF7 Treated with Radicicol and Derivatives of Radicicol
Radicicol
V-25
V-33
V-51
V-27
Percent Growth of Control (%)
120
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Concentration (nM)

FIG.20

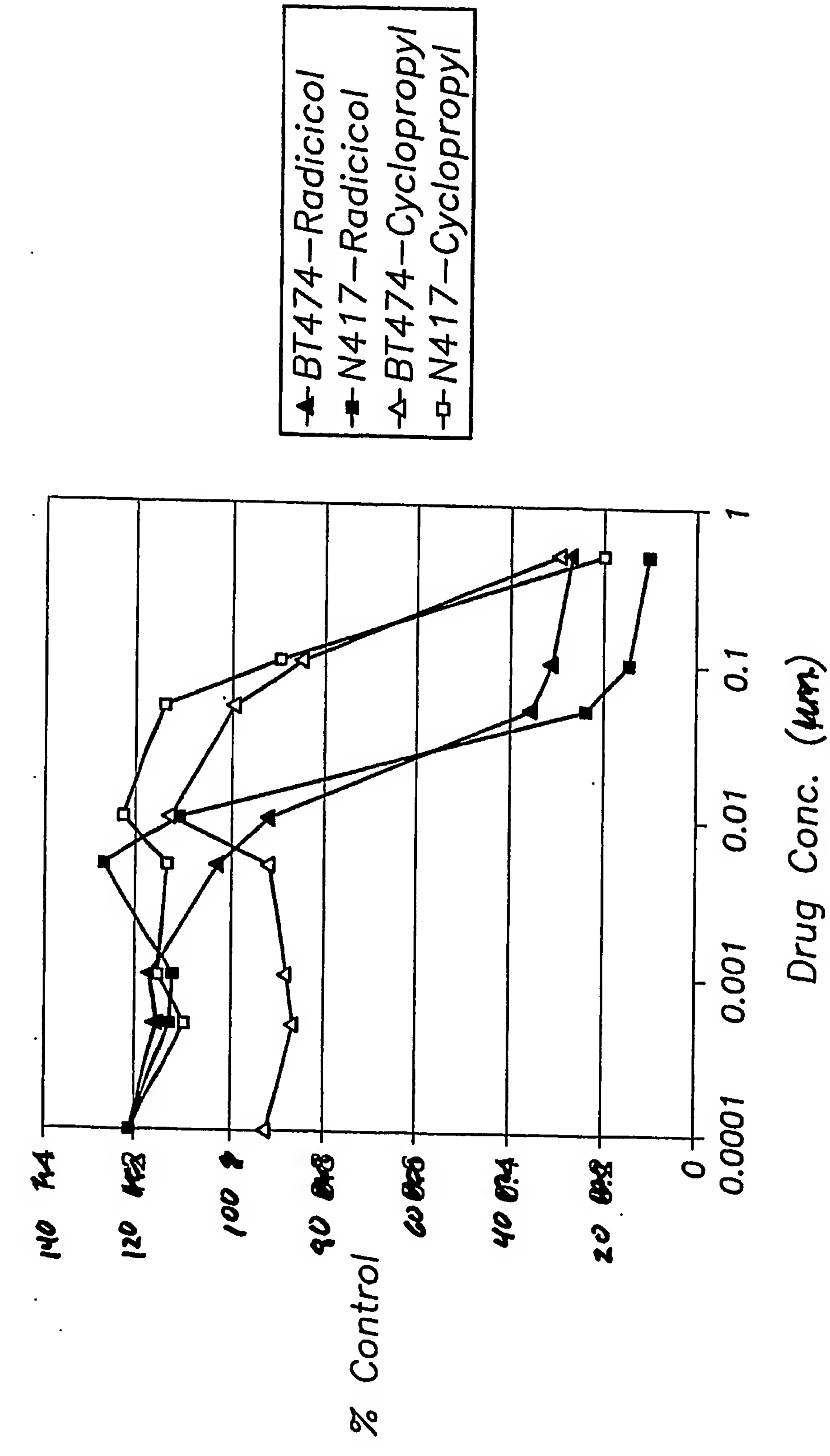
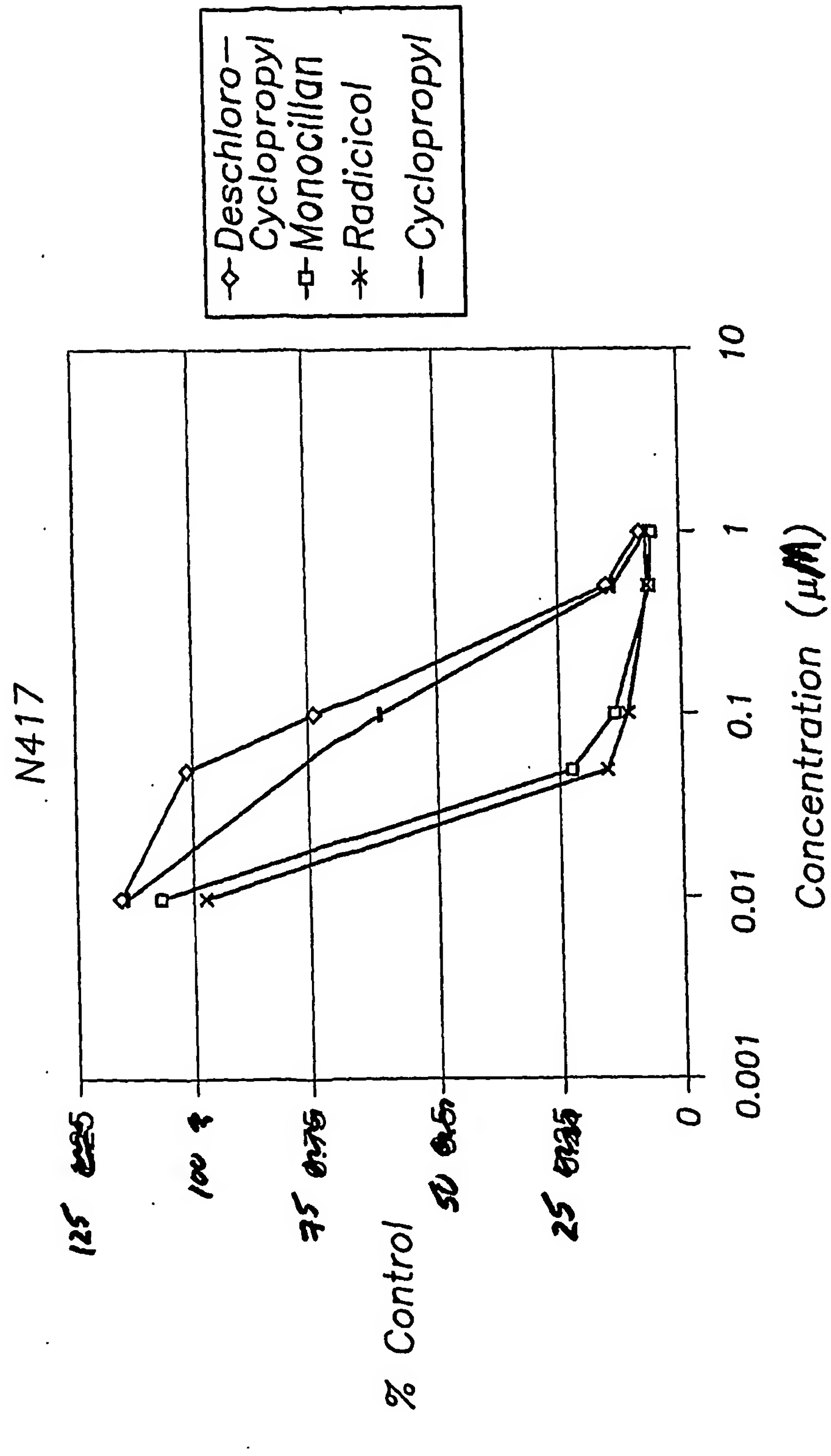

BT474—Radicicol
N417—Radicicol
BT474—Cyclopropyl
N417—Cyclopropyl
% Control
140
120
100
60
40
20
0
0.0001
0.001
0.01
0.1
1
Drug Conc. (µM)

FIG.21


N417
Deschloro—Cyclopropyl
Monocillan
Radicicol
Cyclopropyl
% Control
125
100
75
50
25
0
0.001
0.01
0.1
1
10
Concentration (µM)

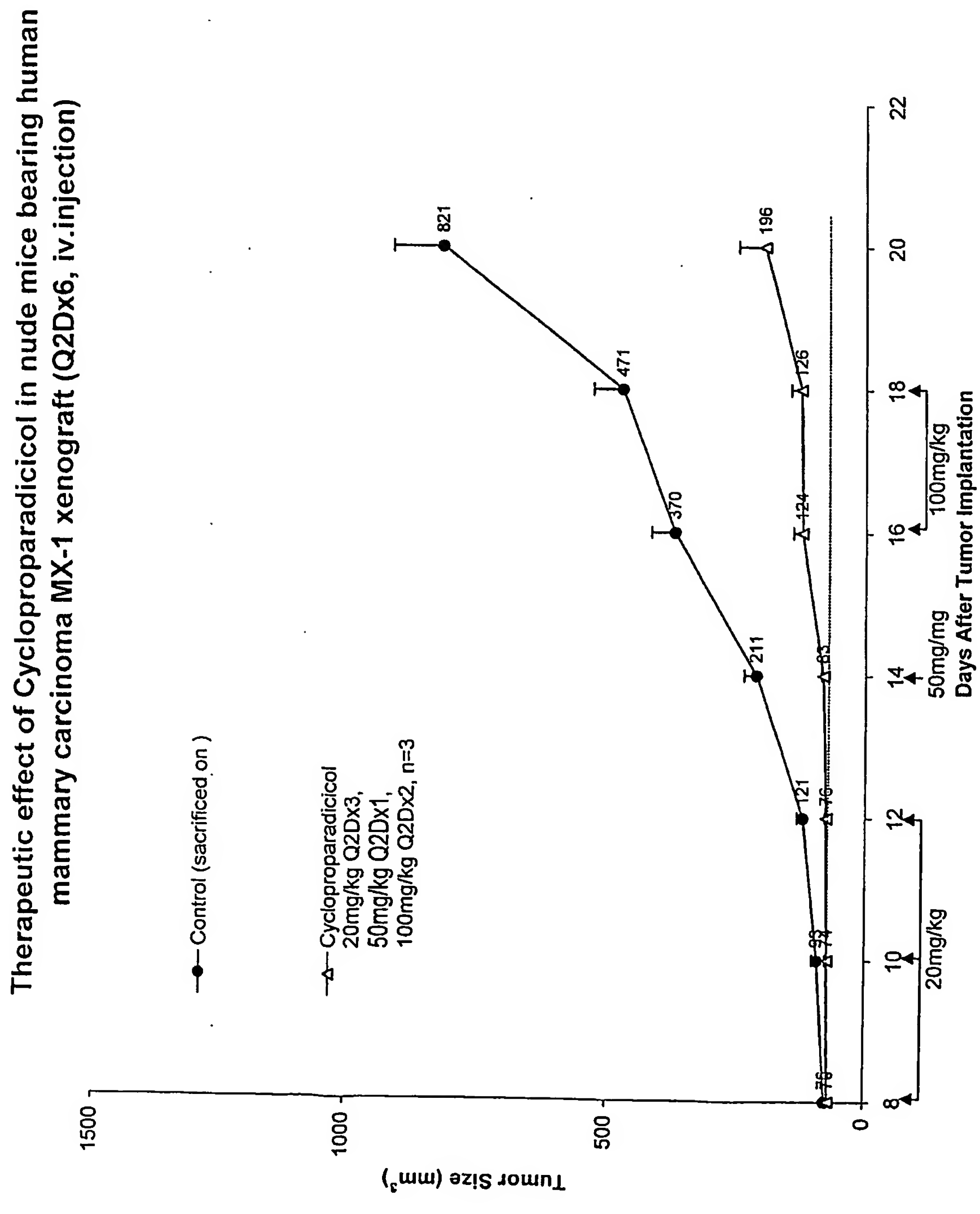

Therapeutic effect of Cycloproparadicicol in nude mice bearing human mammary carcinoma MX-1 xenograft (Q2Dx6, iv.injection)
Control (sacrificed on)
Cycloproparadicicol
20mg/kg Q2Dx3,
50mg/kg Q2Dx1,
100mg/kg Q2Dx2, n=3
Tumor Size (mm³)
1500
1000
500
0
8
10
12
14
16
18
20
22
76
93
74
121
76
211
83
370
124
471
126
821
196
20mg/kg
50mg/mg
100mg/kg
Days After Tumor Implantation

Fig. 22

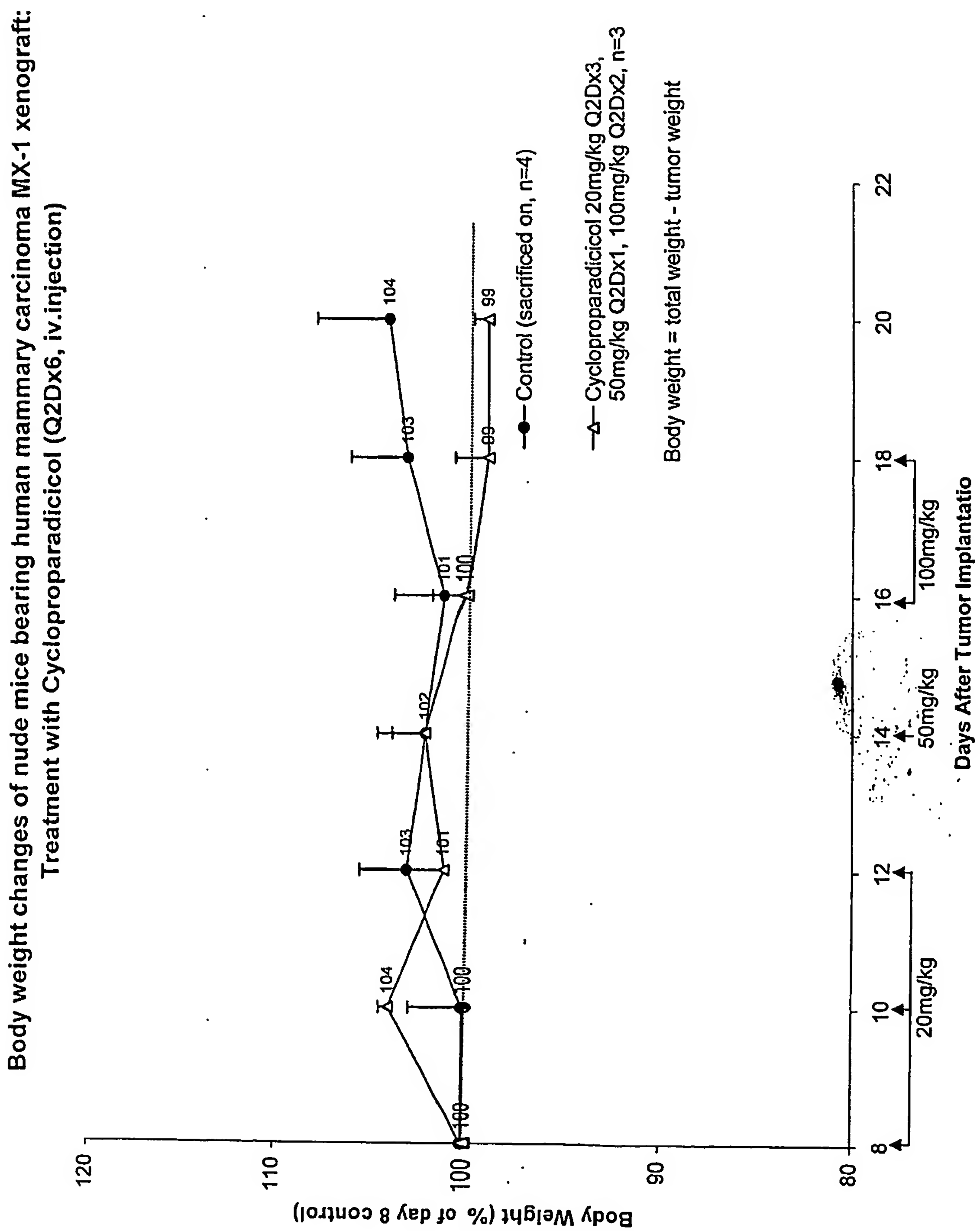

Body weight changes of nude mice bearing human mammary carcinoma MX-1 xenograft:
Treatment with Cycloproparadicicol (Q2Dx6, iv.injection)
Body Weight (% of day 8 control)
120
110
100
90
80
8
10
12
14
16
18
20
22
Days After Tumor Implantatio
20mg/kg
50mg/kg
100mg/kg
100
104
100
103
101
102
101
100
103
99
104
99
Control (sacrificed on, n=4)
Cycloproparadicicol 20mg/kg Q2Dx3, 50mg/kg Q2Dx1, 100mg/kg Q2Dx2, n=3
Body weight = total weight - tumor weight

Fig 23

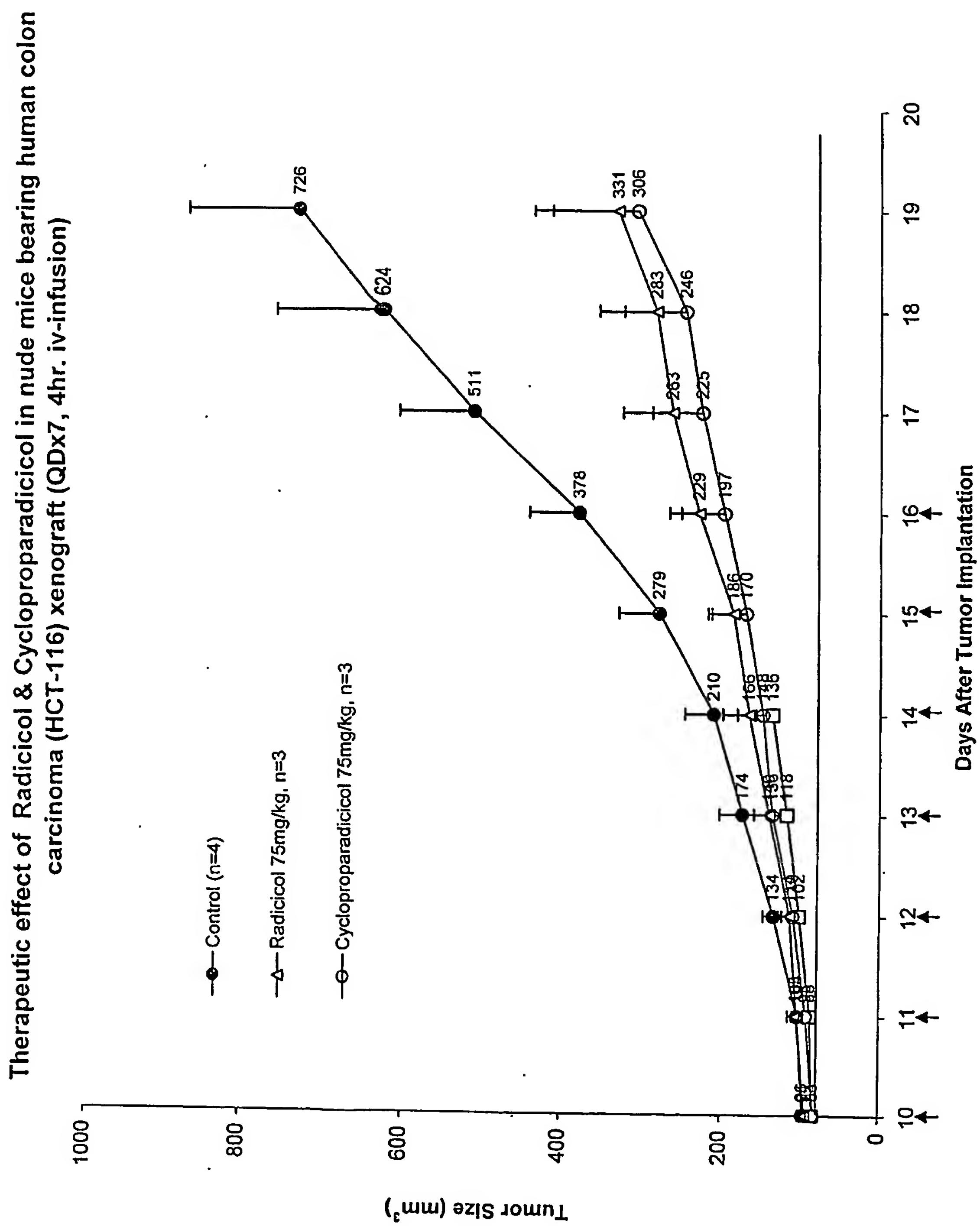

Therapeutic effect of Radicicol & Cyclopropararadicicol in nude mice bearing human colon carcinoma (HCT-116) xenograft (QDx7, 4hr. iv-infusion)
Control (n=4)
Radicicol 75mg/kg, n=3
Cyclopropararadicicol 75mg/kg, n=3
Tumor Size (mm³)
Days After Tumor Implantation
0
200
400
600
800
1000
10
11
12
13
14
15
16
17
18
19
20
726
624
511
378
279
210
174
134
331
306
283
246
263
225
229
197
186
170
166
136
118
102

Fig. 24

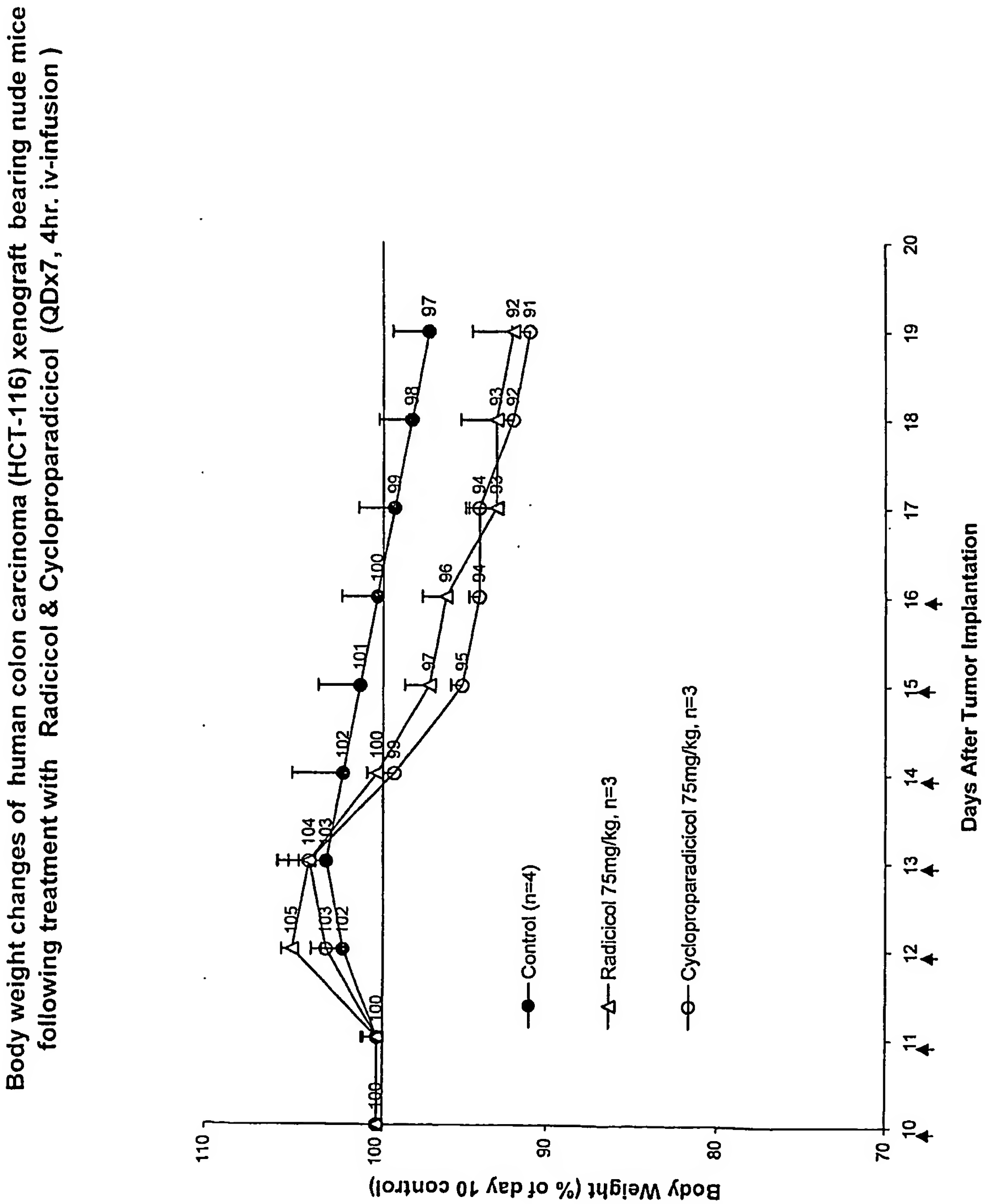

Body weight changes of human colon carcinoma (HCT-116) xenograft bearing nude mice following treatment with Radicicol & Cycloproparadicicol (QDx7, 4hr. iv-infusion)
Body Weight (% of day 10 control)
Days After Tumor Implantation
Control (n=4)
Radicicol 75mg/kg, n=3
Cycloproparadicicol 75mg/kg, n=3

Fig. 25

MX-1 tumors
12 hrs following a 6 hr CIVI

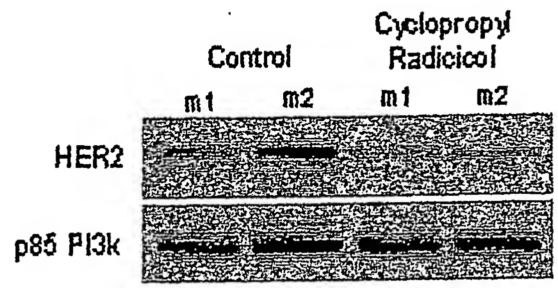
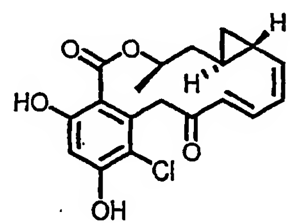
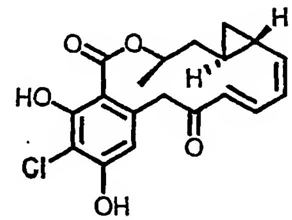
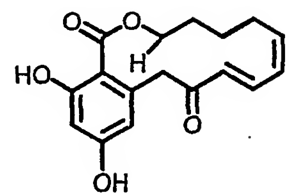


Fig. 26

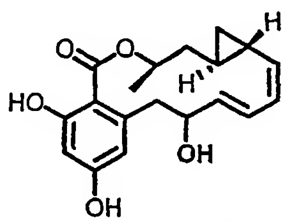
IC_{50} of Growth Inhibition of Different Tumor Cell lines

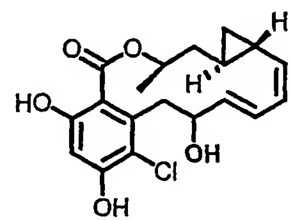


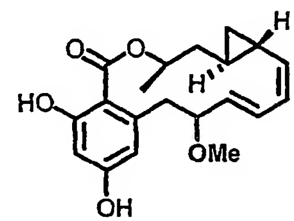




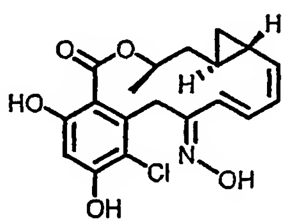
Cell lines			
MCF-7	54 nM	>500 nM	>500 nM
CCRF-CEM	42 nM		
CCRF-CEM/Vinblastin resistant	32 nM		

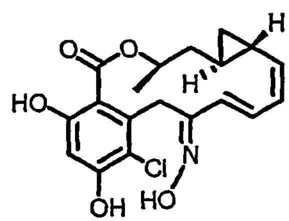






Cell lines			
MCF-7	150 nM, >500 nM	390 nM	>500 nM
CCRF-CEM	208 nM		>5 μM
CCRF-CEM/Vinblastin resistant	209 nM		





Cell lines		
MCF-7	98 nM	282 nM

Fig. 27

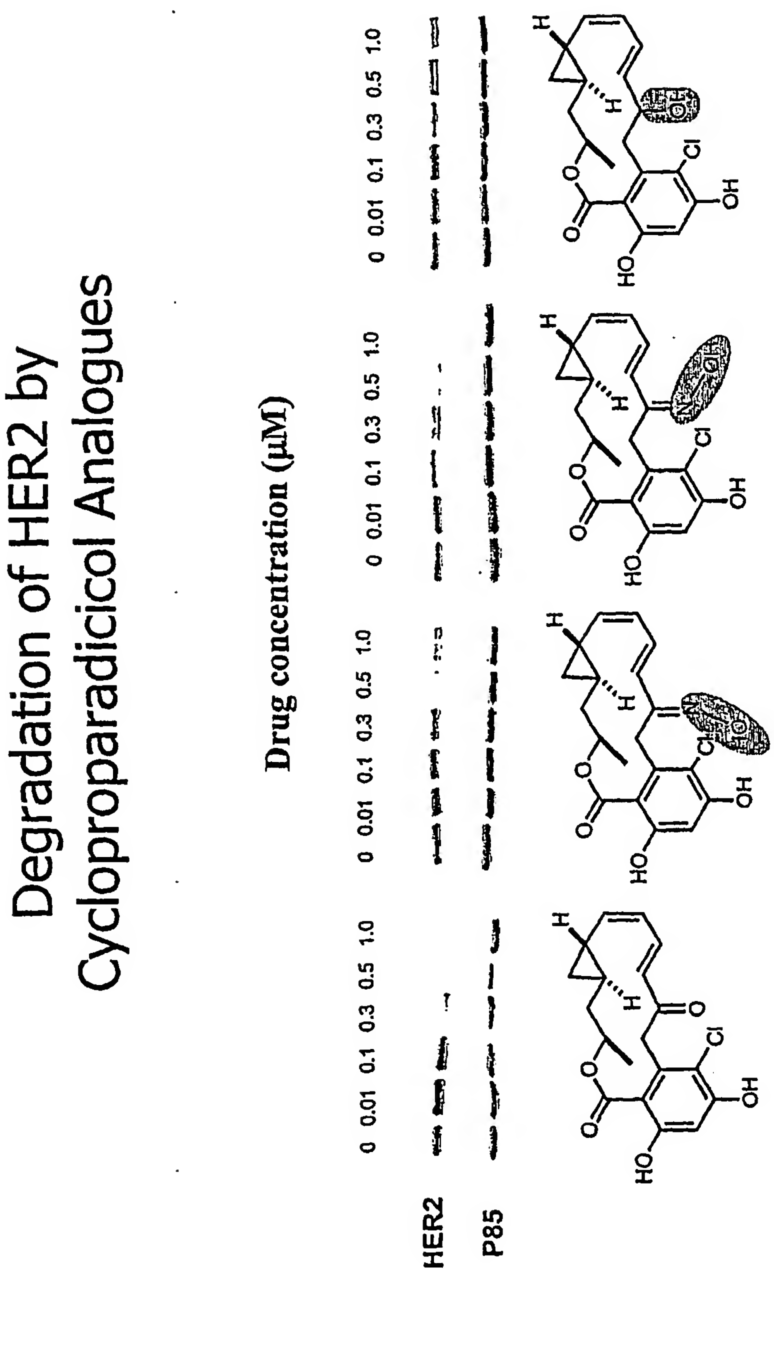

Degradation of HER2 by
Cyclopropradicicol Analogues
Drug concentration (μM)
0 0.01 0.1 0.3 0.5 1.0
0 0.01 0.1 0.3 0.5 1.0
0 0.01 0.1 0.3 0.5 1.0
0 0.01 0.1 0.3 0.5 1.0
HER2
P85

Fig. 28

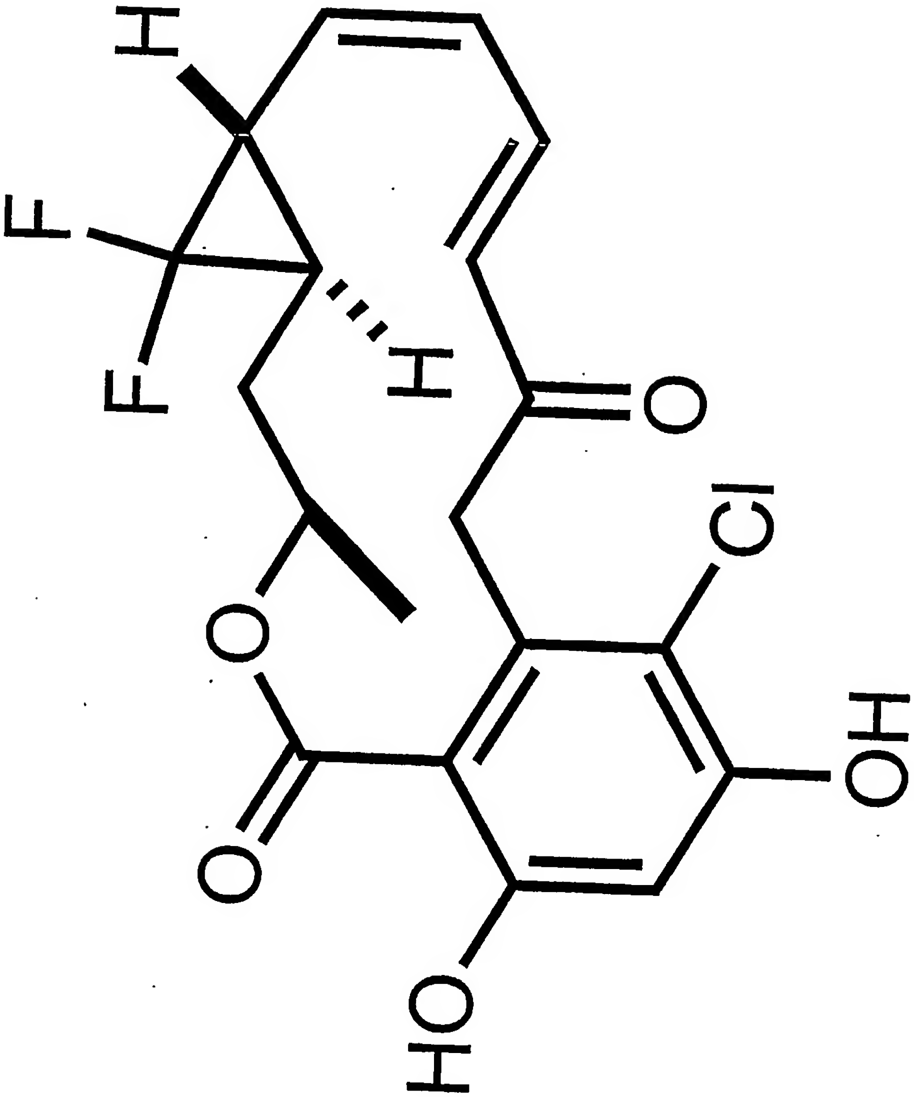


Fig. 29

Cytotoxic effect on CCRF-CEM cell growth by radicicol analogs[a].

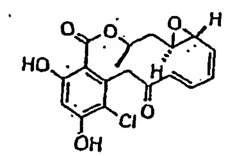
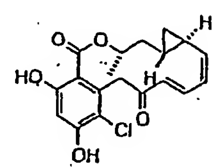
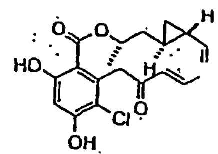
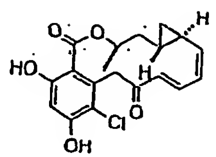
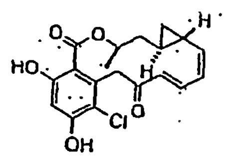
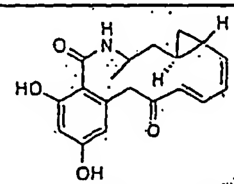
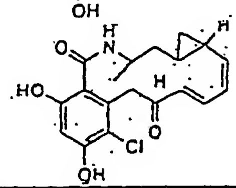
Compound	Structure	Cell growth inhibition (IC_{50} in μM)[b]		
		CCRF-CEM	CCRF-CEM/VBL[c]	CCRF-CEM/taxol[c]
Radicicol (Sigma)		0.055±0.03	0.099 [1.8x]	0.070 [1.3x]
Cyclopropyl 1		4.81	9.84 [2.0x]	7.74 [1.6x]
Cyclopropyl 2		2.34	4.89 [2.1x]	2.89 [1.2x]
Cyclopropyl 3		0.58±0.13	0.87 [1.5x]	0.53 [0.9x]
Cyclopropyl 4 (Cycloproparadicicol)		0.055±0.04	0.041 [0.75x]	0.070 [1.3x]

Fig. 30A

Cytotoxic effect on CCRF-CEM cell growth by radicicol analogs[a]. (Cont'd)

Compound	Structure	Cell growth inhibition (IC_{50} in μM)[b]		
		CCRF-CEM	CCRF-CEM/VBL[c]	CCRF-CEM/taxol[c]
DechloroCyclopropa-radicicol Lactam		>10	>10	ND
Cycloproparadicicol Lactam		>5	>5	ND

a Compounds of radicicol and cycloproparadicicol stereoisomers.

b Cell growth inhibition was measured by XTT tetrazonium assay after 72-hour incubation for cell growth. (Chou et al., Proc. Natl. Acad. Sci. USA 95: 15798-15802, 1998). Five to eight concentrations for each drug were used. IC_{50} values were determined from dose-effect curves by using a computer program CalcuSyn for Windows by Chou and Hayball (Biosoft, Cambridge, UK, 1997).

c CCRF-CEM/VBL and CCRF-CEM/taxol are the CCRF-CEM sublines that are 320-fold and 42-fold resistant to vinblastine and taxol, respectively. Number in brackets is the fold of resistance of each drug when comparing the IC_{50} values with those of the parent cell line, CCRF-CEM. The results showed that radicicol and cycloproparadicicol stereoisomers are not cross-resistant to vinblastine (typical MDR-Pgp substrate) nor to Taxol.

Fig. 30B

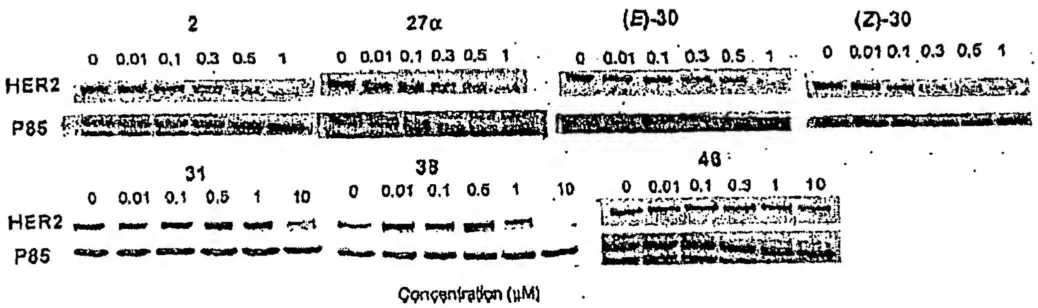


Figure 31: Her2 Degradation Assay